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- Physical and chemical properties of Abestos
- Toxicokinetics and human exposure to Abestos
- Health Effects of Abestos in humans and animals
- Mechanisms of toxicity of Abestos
- Quantification of toxicological effects of Abestos

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
AC	Asbestos cement
BaP	Benzo(a)pyrene
bw	Body weight
D	Diameter
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
HA	Health advisory
i.p.	Intraperitoneal
IR	Intermediate range
L	Length
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PAH	Polynuclear aromatic hydrocarbons
RfD	Reference Dose
s.c.	Subcutaneous
SR	Short range
TWA	Time-weighted average
UICC	Union Internacional Contre le Cancer (International Union Against Cancer)
#fNR	Number of fibers not reported

I. SUMMARY

Asbestos is a generic term referring to a family of naturally-occurring hydrated silicates having a fibrous crystalline structure. Only six fibrous silicates are defined as asbestos fibers and are classified under two basic mineral types: serpentine (chrysotile) and amphibole (actinolite, Cunningtonite-grunerite or amosite, anthophyllite, crocidolite and tremolite). Asbestos fibers are widely used for their noncombustible, nonconducting and chemically-resistant properties. However, since chrysotile, amosite, anthophyllite and crocidolite are of primary commercial importance, most data exist for these fiber types. Comparative solubility as defined by acid resistance is chrysotile < < amosite < actinolite < crocidolite < anthophyllite < tremolite.

Toxicokinetic studies have shown that fibers can penetrate the GI mucosa and thus accumulate in tissues. However, the data indicate that only a small percentage of the fibers ingested are actually involved in penetration and accumulation. Little is known about the metabolism of ingested fibers. The physical and chemical properties of chrysotile and crocidolite fibers have been shown to be altered when exposed to simulated gastric juice. It has been demonstrated that ingested fibers are eliminated through the urine and feces.

Noncarcinogenic toxic effects following acute, subchronic and chronic oral exposures to asbestos fibers are minimal with no specific target organ defined. In animals, the total extent of effects seen were changes in the mucosal lining cells of the ileum along with changes in the colon, rectum and small intestine. In humans, no specific effects have been defined; however, fibers have been detected in body fluids. In vitro test systems have demonstrated cytotoxic properties of asbestos fibers.

Asbestos is considered to be a human carcinogen, EPA weight-of-evidence Group A. The qualitative evidence for human carcinogenicity and the dose-response data base for risk analysis is quite strong for the inhalation exposure route. For exposure by ingestation, the qualitative data base is also strong based on observations from inhalation epidemiology studies and some suggested observations from ingestion epidemiology studies. Some positive responses in the rat confirm that asbestos has the potential for human carcinogenicity by the oral route. However, the suitability and reliability of the data to estimate the carcinogenic risk from exposure to asbestos by ingestion is much weaker than the data base for exposure by inhalation. An NTP bioassay provides a dose-response data base for ingestion as do occupational studies that detected an increased incidence of GI cancer among those persons exposed to airborne asbestos in the workplace. While each of these data bases are limited by uncertainties, the NTP study is seen to be a more reasonable choice for use in the assessment of risk.

Asbestos has not been demonstrated to be mutagenic or teratogenic in animals following oral exposures. No such studies in humans were located in the available literature.

In an attempt to define a mechanism of asbestos toxicity following oral ingestion, it has been demonstrated that fibers interfere with DNA metabo-

II. PHYSICAL AND CHEMICAL PROPERTIES

Asbestos is a generic term referring to a family of naturally-occurring hydrated silicates having a fibrous, crystalline structure widely used for their noncombustible, nonconducting and chemically resistant properties. There are many other minerals that when comminuted, produce fibers; however, most of these other minerals do not possess the above-mentioned properties (Pooley, 1981). A fiber has an aspect ratio (ratio of length to diameter) of 3:1. Compact aerosols with a ratio less than this are usually referred to as particles or dust. Asbestos cleaves along the longitudinal axis and therefore separates into smaller fibrils when subjected to mechanical action.

The asbestos minerals are divided into two classes based on their chemical and physical properties: the serpentines and the amphiboles (Table II-1). Only six fibrous silicates are defined as asbestos fibers classified as: chrysotile (serpentine), and crocidolite, amosite (also known as Cunningtonite-grunerite), anthophyllite, actinolite and tremolite (amphibole).

The two basic mineral types, serpentine and amphibole, consist of hydrated silicates in a complex crystal system. The general chemical composition of the individual types of asbestos are provided in Table II-2. It should be noted, however, that the values obtained from actual chemical analysis of samples may differ slightly from these typical formulae. The individual fibers are discussed in the following sections. Chrysotile is the most abundant form of asbestos. Chrysotile, amosite, anthophyllite and crocidolite are the commercially important fibers (IARC, 1976). Additional lism in rat tissues of the GI tract and other organs. Impaired active transport of glucose across membranes and cytotoxic effects have also been demonstrated. Following an evaluation of _in vitro_ tests, it has been concluded that the role of asbestos fibers in the carcinogenesis process in the respiratory tract is one of tumor promotion or cocarcinogenesis versus that of initiation. This is supported by the _in vitro_ tests conducted on PAHs and asbestos fibers.

It has been suggested that asbestos fibers and PAHs may act as cocarcinogens in the causation of lung cancer. This is based on the observations made on the effects of asbestos on B[a]P transport and metabolism. Asbestos mediates a rapid transport of B[a]P across cellular membranes and appears to alter B[a]P metabolism and activity of aryl hydrocarbon hydroxylase in a number of cell types. The relevance of these factors to the ingestion of asbestos has not been established.

Toxicological data are insufficient to derive 1-day and 10-day HAs for a child. It is also considered prudent not to derive longer-term HAs or a DWEL since the endpoint toxicity from inhaled asbestos exposure is carcinogenicity and the latent period for cancer manifestation from occupational exposure is in the magnitude of ≥ 20 years.

Three animal studies demonstrated that asbestos fibers can be associated with GI tumorgenicity (both benign and malignant). Chrysotile and amosite seem to produce a response in rats although the responsibility is not clear. For a ligetime individual risk of 10^{-6}, the maximum likelihood estimate of concentration is $1.3\text{x}10^{7}$ f/ℓ with a 95% lower limit of $7.1\text{x}10^{6}$ f/ℓ.

TABLE II-1

Classification of Asbestos Minerals*

	CLASS	
	Serpentine	Amphibole
Major types	chrysotile	actinolite, amosite, anthophyllite, crocidolite, tremolite
Basic composition	hydrated magnesium silicate	various silicates of iron, sodium, magnesium and calcium
General physical nature of fiber	pliable, curly	rodlike, straight
General texture of fiber	silky, soft	harsh, stiff
Properties	alkali resistant	acid resistant

*Source: Adapted from Pooley, 1981

In general, the resistance to acid solution is chrysotile << amosite < actinolite < crocidolite < anthophyllite < tremolite (NAS, 1977).

TABLE II-2

Chemical Structure of the Asbestos Fibers[a]

Type	X Site Cations[b]	Y Site Cations[c]	General Chemical Formula
Serpentine - chrysotile	NA	NA	$Mg_3Si_2O_5(OH)_4$
Amphibole - actinolite	Mg,Fe^{2+}	Ca	$Ca_2(Fe^{2+},Mg)_5Si_8O_{22}(OH)_2$
- amosite	Fe^{2+},Mg	Fe^{2+},Mg	$(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$
- anthophyllite	Mg,Fe^{2+}	Mg,Fe^{2+}	$(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$
- crocidolite	Fe^{2+},Fe^{3+},Mg	Na	$Na_2(Mg,Fe^{3+},Fe^{2+})Si_8O_{22}(OH)$
- tremolite	Mg,Fe^{2+}	Ca	$Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$

[a] Source: Adapted from Pooley, 1981

[b] X site cations link Si_4O_{11} chains into pairs

[c] Y site cations link the pairs of chains

NA = Not applicable

NOTE: Where cations are written in parentheses without subscripts, a variable composition is indicated with the most predominant species first.

physical and chemical properties on these four fiber types are provided in Table II-3. An extensive review of the properties of different types of asbestos is avilable in Drury et al. (1977).

Serpentine Asbestos Fibers

Properties of Chrysotile Asbestos. The crystalline structure of the serpentine form of asbestos differs from that of the amphibole varieties. Chrysotile consists of a continuous sheet of silicon-oxygen tetrahedra connected in sandwich fashion to a brucite (magnesium hydroxide) layer in which two of every three hydroxyl groups are replaced by apical oxygens of the silica tetrahedra. The resulting twin-layered sheet (Figure II-1) is strained because of a mismatch between the different dimensions of the brucite and silica sheets. This strain is relieved by curling of the twin-layered sheet with the silica layer innermost (Speil and Leineweber, 1969). Chrysotile fibrils thus consist of scrolls or cylindrical forms having several convolutions. Typically, individual fibrils are long, flexible and curved, and they tend to form bundles that are often curvilinear with splayed ends. Visible chrysotile fibers consist of large aggregates of such bundles weakly associated through hydrogen bonding or physical means (extrafibril solid matter). In transmission electron micrographs, most chrysotile fibrils appear to have a central capillary surrounded by an electron-dense wall. The dimensions of chrysotile fibers depend on the extent to which the sample has been "opened" or dissociated into individual fibrils. In massive form, chrysotile fibers occur in lengths varying from 1-20 mm, with occasional samples as long as 100 mm. After milling, the lengths of typical commercial grade fibrils vary from 1-2 mm and fibril diameters range from 10-80 nm, with mean values of various grades generally falling in the range of 30-38 nm (Atkinson et al., 1971). Although these

TABLE II-3

General Physical and Chemical Properties
of Chrysotile, Amosite, Anthophyllite and Crocidolite*

Property	Chrysotile	Amosite	Anthophyllite	Crocidolite
Mineral association	in altered peridotite adjacent to serpentine and limestone near contact with basic igneous rocks	in crystalline schists, etc. branded ironstones	in crystalline schists and gneisses	iron-rich silicious argillite in quartzose schists branded ironstones
Color	white, grey, green, yellowish	ash grey, greenish or brown	greyish, white brown-grey or green	Lavender, blue, greenish
Hardness (MOHS scale)	2.5-4.0	5.5-6.0	5.5-6.0	4
Specific Gravity	2.55	3.43	2.85-3.1	3.37
Tensile strength (kg/cm²)	31,000	25,000	<5,000	35,000
Young's modulus (kg/cm²)	1.65×10^6	1.65×10^6	--	1.9×10^6
Length	short to long	long	short	short to long
Fusibility	fusible at 1710°C	fusible at 1575°C loses water at moderate temperatures	fusible at 1650°C	fusible at 1335°C

TABLE II-3 (cont.)

Property	Chrysotile	Amosite	Anthophyllite	Crocidolite
Cleavage	010 perfect	210 perfect	210 perfect	210 perfect
Extinction	parallel	parallel	parallel	parallel
Birefringence	moderate first-order	strong second-order	moderate low second-order	weak (masked)
Refractive Index (7α)	1.493-1.553	1.657-1.688	1.578-1.652	1.685-1.698
Refractive Index (7γ)	1.517-1.557	1.657-1.717	1.591-1.676	1.689-1.703
Electric charge	+	-	-	-
Maximum solubility in HCl: % loss in weight	56.00	12.00	2.13	3.14
Maximum solubility in NaOH: % loss in weight	1.03	6.82	1.77	1.20

*Source: Adapted from IARC, 1976

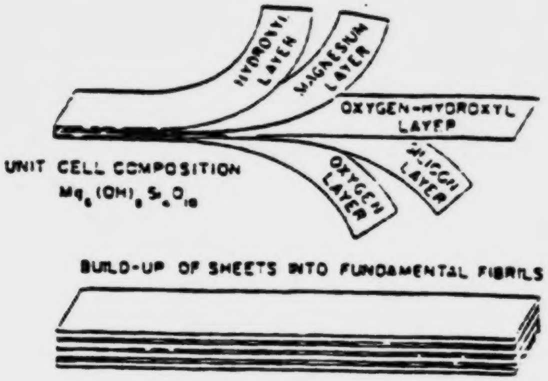


FIGURE II-1

Fundamental Sheet of Chrysotile

Source: Spell and Leineweber, 1969

fibers are small, they have great tensile strength; typical values range from 30,600-44,800 kg/cm² for samples 0.3-3.0 cm long. Consequently, chrysotile fibers are frequently used as a reinforcing agent in cement, paper and plastic products. Because of their small diameters and porous surfaces, these fibers also have extremely large surface areas (from ~15-88 m²/g, depending on sample type and pretreatment). This characteristic is important for filtration and reinforcement applications as well as for uses involving aqueous dispersions in the presence of surface active agents such as sodium laurate and dodecylbenzenesulfonate.

Impurities of Chrysotile Asbestos. The empirical formula for chrysotile asbestos is $Mg_3Si_2O_5(OH)_4$. Although this formula may vary slightly from sample to sample, it is nonetheless closely approached by the majority of commercially milled or processed chrysotile fibers. A number of naturally occurring impurities have been identified in commercial chrysotile samples. The most common mineral impurities are brucite, chlorite, talc, various carbonates, magnetite and quartz; principal metallic impurities include iron, chromium, nickel and manganese. Although virgin chrysotile, in contrast to the amphiboles, is not associated with primary oil or organic impurities, contaminants of this nature have been frequently observed in processed fibers. These impurities are believed to have resulted through exposure of the fibers to contaminants during processing, manufacturing or through storage.

Reactions and Decomposition. Since the outer surface of a chrysotile fiber is essentially composed of magnesium hydroxide (brucite), chrysotile is highly susceptible to acid attack. Exposure to mineral acids results in the liberation of magnesium ions and the formation of a silicous residue.

Chrysotile fibers are almost completely destroyed within 1 hour when placed in 1 N HCl at 95°C. Amphibole fibers are considerably more resistant to mineral acids than are chrysotile fibers (Lindell, 1972). In contrast to the high vulnerability of chrysotile asbestos to acids, however, chrysotile is more resistant to attack by sodium hydroxide than any of the amphibole fibers.

Although asbestos has been widely used as a fireproof material, all varieties of fibers have been shown to undergo thermal decomposition commencing in the 150-200°C range. Thermal decomposition occurs through dehydroxylation and dehydration mechanisms. Under dynamic heating conditions, dehydroxylation occurs at ~650°C, and formation of fosterite and silica is apparent at ~810°C (Speil and Leineweber, 1969). The insulating properties of asbestos are a result of its fibrous structure and the poor thermal conductivity of the individual fibers.

Amphibole Asbestos Fibers

While chrysotile asbestos is considered to be a distinct mineral, the five amphiboles are varieties of other minerals (Zoltai and Stout, 1976). Each of the amphiboles is distinct from the others, differing in both chemical and physical properties. As a commonality, however, they all contain silicon and all form fibers when crushed (U.S. EPA, 1980).

The basic crystal structure of the amphibole minerals is less complicated than that of the serpentine chrysotile. The basic amphibole structure is that of a double silica chain. As is the case with the chrysotile sheets, the silica tetrahedra all point in a common direction. However, in the amphiboles the chains are paired in "back-to-back" fashion, separated by a layer of cations to complement the negative charges of the silica chains (Figure II-2). Magnesium, iron, calcium and sodium have been reported as principal cations in amphibole structure.

All amphibole asbestiform fibers have the same basic crystal structure, double chains of linked tetrahedra that have the unit composition $(Si_4O_{11})_n$ along the fiber axis. Massive forms of amphibole asbestiform fibers consist of numerous paired chains stacked in an ordered array. The various amphibole asbestiform fibers differ essentially only in the nature of the cations occupying the intraskeletal cation sites. However, the amphibole structure allows great flexibility in cation replacement, and various amphibole asbestiform fibers exhibit a wide range of chemical compositions and physical properties. Only rarely does the composition of a field sample coincide with the assigned theoretical or idealized formula. However, theoretical compositions are used for identifying the various fibers as a matter of convenience.

While the crystal structure of amphiboles is less complex than that of chrysotile, the chemical composition of the asbestiform amphiboles is more complex. Table II-4 provides an indication of the composition and variability of the five amphibole asbestos types.

Properties and common contaminants of specific asbestiform amphiboles are presented in the following discussion.

Properties of Crocidolite Asbestos. Crocidolite, second only to chrysotile in commercial importance among the various asbestiform minerals, is represented by the general chemical formula $Na_2(Mg,Fe^{3+},Fe^{2+})Si_8O_{22}(OH)$.

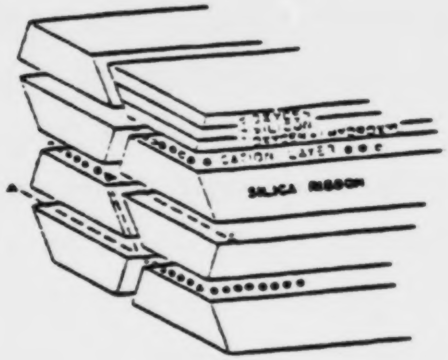


FIGURE II-2

Amphibole Structure

Source: Speil and Leineweber, 1969

TABLE II-4

Chemical Composition of Asbestiform Amphiboles*

	Asbestiform Amphibole (range %)				
	Crocidolite	Amosite	Anthophyllite	Actinolite	Tremolite
SiO_2	49-53	49-53	56-58	51-56	55-60
MgO	0-3	1-7	28-34	15-20	21-26
FeO	13-20	34-44	3-12	5-15	0-4
Fe_2O_3	17-20	---	---	0-3	0-0.5
Al_2O_3	0-0.2	---	0.5-1.5	1.5-3	0-2.5
CaO	0.3-2.7	---	---	10-12	11-13
K_2O	0-0.4	0-0.4	---	0-0.5	0-0.6
Na_2O	4.0-8.5	trace	---	0.5-1.5	0-1.5
H_2O	2.5-4.5	2.5-4.5	1.0-6.0	1.5-2.5	0.5-2.5

*Source: Speil and Leineweber, 1969

Typical crocidolite fiber bundles easily disperse into long, delicate, blue-green fibrils that are elliptical or nearly circular in cross section. Crocidolite fibrils are shorter and thinner than other amphibole asbestiform fibers, but not as short as those of chrysotile. However, the dimension and coarseness of crocidolite varies by geographic locations (Wagner et al., 1960). The modal diameter and length of the Union Internacional Contre le Cancer (UICC) standard reference samples of crocidolite, ultrasonically dispersed in water, are 0.13 μm and 0.6 μm, respectively (Langer, et al., 1974). Crocidolite fibers are the strongest of the amphiboles, with a tensile strength of ~30,000 kg/cm² for a "typical" sample. The surface area of each of the five varieties of amphibole asbestos fibers is substantially less than that of chrysotile. Crocidolite fibers generally have surface areas in the 5-15 m²/g range, depending on the nature of pretreatment of the sample. In distilled water at pH 7.4., the surface charge (zeta potential) of amphibole fibrils is negative and smaller in magnitude than the positive charge on chrysotile fibrils. The complementary nature of these two asbestos types is utilized advantageously in the asbestos cement industry by blending crocidolite and chrysotile fibrils to achieve optimal sedimentation and filtration rates. In comparison with other amphiboles or chrysotile, crocidolite has relatively poor resistance to heat, but its fibers are used extensively in applications requiring good resistance to acids or sea water. Crocidolite fibers have fair to good flexibility, fair spinnability, and a texture ranging from soft to harsh. Unlike chrysotile, crocidolite is usually associated with organic impurities, including low levels of carcinogenic, PAHs such as BaP.

Properties of Amosite Asbestos. Amosite is a fibrous, monoclinic form of the amphibole grunerite, which ranks next to crocidolite in commercial importance. The general chemical formula for amosite is $(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$; the Fe^{2+} to Mg ratio varies but typically is 5:2. Amosite fibrils are generally larger than those of crocidolite but smaller than particles of anthophyllite fibers. Most amosite fibrils have straight edges and characteristic right-angle fiber axis terminations. The modal diameter and length of UICC standard reference amosite ultrasonically dispersed in water are 0.14 µm and 1.4 µm, respectively, (Langer et al., 1974). Amosite fibril bundles have roughly half the tensile strength attributed to crocidolite fibers and are less resistant to chemical attack than any of the other amphibole asbestiform fibers except actinolite. Unlike crocidolite, however, amosite has good heat resistance, and ~84% of the reported U.S. consumption of this fiber is used for thermal insulation. Like other amphibole asbestiform fibers, virgin amosite characteristically contains small quantities of extractable organic matter, including traces of the carcinogen B[a]P.

Properties of Anthophyllite Asbestos. Anthophyllite is a relatively rare, fibrous, orthorhombic, magnesium-iron amphibole that is currently produced in commercial quantities only in the Paakkola area of Finland. Its general chemical formula is $(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$, where the Mg to Fe^{2+} ratio is variable, but large, with Mg being the predominant species. Typically, anthophyllite fibrils are more massive than other common forms of asbestos. The modal diameter and length of the UICC standard reference material ultrasonically dispersed in water are 0.18 µm and 5.1 µm, respectively (Langer et al., 1974). The tensile strength of anthophyllite fibers is inferior to that of all the other forms of asbestos except tremolite, and its harsh texture, short length and brittle nature limit its use in spun fiber. However, anthophyllite fibers have good resistance to heat and are moderately attractive as a filter medium.

Properties of Actinolite and Tremolite Asbestos. The remaining types of common asbestiform fibers include tremolite, the monoclinic calcium-magnesium amphibole, and its predominantly iron-substituted derivative, actinolite. Tremolite has the general chemical formula $Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$. The formula for actinolite is similar except that part of the magnesium is preferentially replaced by iron(II) cations: $Ca_2(Fe^{2+},Mg)_5Si_8O_{22}(OH)_2$. The modal diameter and length of the UICC standard reference sample of tremolite ultrasonically dispersed in water are 0.17 µm and 5.1 µm, respectively. Tremolite forms fibrils more massive than those of either crocidolite or amosite, but comparable with those of anthophyllite. In electron micrographs these fibrils exhibit characteristic irregularities in edges and ends. Although tremolite fibrils are the lowest in tensile strength of all the common types of asbestos, they exhibit good resistance to chemical attack by both acids and alkalis. The tensile strength of actinolite is ~4 times greater than that of tremolite, but it is the most vulnerable of all the amphibole asbestiform fibers to attack by acids and alkalis. Currently, neither actinolite nor tremolite is produced commercially, and little information exists concerning their mining activities, uses, or physical and chemical properties; however, Canadian chrysotile contains small amounts of tremolite (Craighead and Mossman, 1982). Tremolite is also found as a contaminant in certain talc deposits that have been used in some talcum powders (Selikoff et al., 1973). Until recently there was no attempt to remove tremolite from talc during milling.

Summary

Only six fibrous silicates are classified as asbestos fibers based on specific physical properties including heat resistance and the ability to be woven (Pooley, 1981). These fibers are classed under two basic mineral types: serpentine (chrysotile fiber) and amphibole (actinolite, amosite, anthophyllite, tremolite and actinolite fibers). Only chrysotile, crocidolite, amosite and anthophyllite are of commercial importance; thus, most data exist for these fibers. Chemical composition of the individual fibers will vary with point of origin; however, the serpentine chrysotile is most distinct from the five amphibole asbestos fibers. Chrysotile is a hydrated magnesium silicate whereas the amphiboles are silicates of iron, sodium, magnesium and calcium. Comparative solubility as defined by resistance to acid solution is chrysotile << amosite < actinolite < crocidolite < anthophyllite < tremolite.

III. TOXICOKINETICS

Absorption and Distribution

Ingestion of Asbestos. Exposure to asbestos by ingestion may occur through drinking water, recreational water, foods and beverages contaminated with asbestiform fibers, or through the swallowing of fibers cleared from the respiratory passages by mucocilliary activity. It has also been postulated that inhaled asbestos may migrate across the lung parenchyma to other organs. Thus, asbestos might ultimately reach the GI tract either directly by ingestion or indirectly from the lungs through the vascular or lymphatic systems. The review of toxicokinetics in this chapter will focus only on direct ingestion or GI instillation and will not include postulated indirect transport from the lungs.

A vital question in the determination of the significance of ingestion to potential pathogenicity is whether asbestos actually migrates across the intestinal mucosa and enters the blood or lymphatic circulation -- a condition that would permit both the embedding of fibers in the intestinal wall and transport to other organs and tissues of the body. Such movement of fibers is a likely precursor of carcinogenesis following the ingestion of asbestos (Cook, 1983). The question of GI migration, following ingestion or instillation in the GI tract, has been studied by a number of independent researchers. Cook (1983) reviewed the literature and critically evaluated each study to assess the significance of their findings. Biological, analytical, mineralogical and kinetic factors were considered.

It is obvious from Table III-1 that the preponderance of evidence seems to be in favor of transmigration of asbestos through the GI wall. In addition, a number of investigators have addressed this issue by displaying

TABLE III-1

Summary of Studies on Fiber Penetration of the Gastrointestinal Mucosa[a]

Evi-dence for/ Against	Species	No. Exam-ined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed[b]	Tissue Preparation Method[c]	Microscope Technique	Detection Limit Reported	Positive/ Negative Control Samples	Reference
+	Rat	3	chryso-tile	no characteri-zation, 6% diet	3 mo	colon (+) mesenteric nodes (-) spleen (-)	thin sections	TEM	no, quali-tative	no/no	Westlake et al., 1965
+	Rat	5 5 5	chryso-tile chryso-tile control	9.4×10^6 fibers 94×10^6 fibers no fibers	stomach injection	blood (+) omentum (+) brain (+) lung (-) spleen (-) heart (-)	bulk, soluene, centr HTA, drop HTA, drop	TEM	no	no/con-taminated	Cunningham and Pontefract, 1973; Pontefract and Cunningham, 1973
-	Rat	10 5	chryso-tile control	no characteri-zation, 5% diet no fibers	21 mo	intestine (-) mesentery (-) other organs (-)	bulk, bleach, centr, wash, drop	TEM	incomplete	no/con-taminated	Gross et al., 1974
	Rat	10 10 5	amosite tailings control	no characteri-zation, 400 mg no fibers	single gavage	intestine (+) mesentery (-) lung (?) kidney (-)	bulk, bleach, centr, wash, drop	TEM	no	no/yes	
	Rat	10 10 10	amosite tailings control	no characteri-zation, 10, 20% diet no fibers	6 days	intestine (-) mesentery (?) lung (-) kidney (-)	bulk, bleach, centr, wash, drop	TEM	no	no/yes	
-	Rat	2 2 2 2	chryso-tile croci-dolite amosite control	UICC 250-300 mg/wk average consumption in margarine no fibers	1 yr + 1 mo free from exposure	GI tract (-)	bulk, HTA, acid, filt	SEM	incomplete, semiquali-tative	no/yes	Bolton and Davis, 1976

TABLE III-1 (cont.)

Evidence for/Against	Species	No. Examined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed^b	Tissue Preparation Method^c	Microscope Technique	Detection Limit Reported	Positive/Negative Control Samples	Reference
+	Rat	10 10	chrysotile control	fiber size only, 1% diet no fibers	6 wk	blood (?) omentum (+) lung (+) kidney (+) liver ( ) brain (+)	bulk, LTA, acid, filt, LTA, drop	TEM	no	no/contaminated (less than 1973)	Cunningham et al., 1977
+	Rat	5 2	amosite control	UICC, 0.1 mg saline	1 hr in isolated jejunum segment	epithelial surface penetration (+)	SEM preparation	SEM	qualitative	no/yes	Storeygard and Brown, 1977
-	Human	282	asbestos bodies	no characterization		lung (+)	bulk, LTA	OM	incomplete	yes/no	Auerbach et al., 1977
+	Human	8 8	amphibole control	10^6 fibers/ℓ in water <10^6 fibers/ℓ in water	variable by subject	urine (+)	bulk, filt, LTA, filt, c-coat, wick	TEM	~10 fibers/mℓ	yes/yes	Cook and Olson, 1979
+	Baboon neonate	1 1	chrysotile control	ca. 3×10^{12} fibers in milk no fibers	9-day period	kidney (+) liver (-) spleen (-)	bulk, LTA, filt, LTA filt, drop	TEM	~80 fibers/mg	no/yes	Patel-Mandlik et al., 1979
+	Baboon	1	chrysotile	UICC, 120 kg pregavage	4 days gavage	urine (+)	bulk, filt, LTA, filt, LTA, drop	TEM	5×10^2 fibers/mℓ	no/yes	Hallenbeck and Patel-Mandlik, 1979
+	Human	53^d	amphibole chrysotile	10^6 fibers/ℓ in water none in water	variable by subject	liver (+) lung (+) jejunum (+)	bulk, KOH, centr HTA, drop	TEM	30 fibers/mg	yes/yes	Carter and Taylor, 1980
+	Rat	5 5 15 8 2	chrysotile crocidolite chrysotile chrysotile control	UICC, ~10^{11} fibers UICC, ~10^{10} fibers NIEHS 10^{11} to 10^{12} fibers NIEHS 10^{10} to 10^{11} fibers no fibers	single gavage single gavage diet <1-12 days diet <1-12 days	lymph fluid (+) lymph fluid (+) lymph fluid (+) lymph fluid (+) lymph fluid (+)	bulk, digestion, filt, c-coat, wick	TEM	incomplete	no/yes	Sebastien et al., 1980

TABLE III-1 (cont.)

Evidence For/Against	Species	No. Examined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed[b]	Tissue Preparation Method[c]	Microscope Technique	Detection Limit Reported	Positive/Negative Control Samples	Reference
+	Rat	10	chrysotile	UICC, 10% diet	2 yr	colon (+)	thin, 20 μm, HTA	TEM	no	no/yes	Donham et al., 1980
		10	cellulose	cellulose fibers		colon (-)					
		6	control	no fibers		colon (-)					
+	Baboon newborn	1	chrysotile	UICC, $3x10^{10}$ fibers/kg bw	9-day period	kidney cortex (+) lymph nodes (+) spleen (+) colon (+) esophagus (+) kidney medula (+) other sites (-)	bulk, LTA, filt, LTA, drop		~80 fibers/mg	no/yes	Patel-Mandlik and Millette, 1980
		1	control	no fibers							
+	Human	34	chrysotile	none in drinking water	unknown	urine (+)[e]	bulk, filt, LTA, filt, c-coat, wick	TEM	~10 fibers/mℓ	no/yes	Cook and Longrie, 1981
+	Human	1	attapulgite	5 g/day	drug, 6 mo	urine (+)	bulk, undefined	TEM	no	no/yes	Bignon et al., 1981
	Baboon	1	chrysotile	NIEHS, 800 mg	gavage, 8 times	urine (-) blood (-)	bulk, filt, LTA, acetone, drop	TEM	~$4x10^3$ f/mℓ ~$4x10^4$ f/mℓ	yes/yes	Hallenbeck et al., 1981
			crocidolite	NIEHS, 800 mg		tissues (-)	bulk, KOH, filt, LTA, acetone drop		200 f/mg		
		1	control	no fibers							
+	Fish	2	amphibole	ca. 10^8 fibers/ℓ	lifetime, water and possibly diet	kidney (+)[f] liver (+) muscle (+)	bulk, LTA, filt, c-coat, wick	TEM	1-10 f/mg	no/yes	Batterman and Cook, 1981
		1	amphibole	ca. 10^6 fibers/ℓ							
		2	chrysotile	unknown							

TABLE III-1 (cont.)

Evidence For/Against	Species	No. Examined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed[b]	Tissue Preparation Method[c]	Microscope Technique	Detection Limit Reported	Positive/Negative Control Samples	Reference
-	Rat	13	chrysotile	UICC, 250 mg/wk in margarine	24.5 mo	9 sites (-)[g]	bulk, LTA, acid, filt	SEM	incomplete	no/no	Bolton et al., 1982
		12	amosite								
		13	crocidolite								

[a] Source: Cook, 1983

[b] Positive or negative for fibers

[c] Preparation method steps: thin = removal of a thin tissue section for examination; bulk = processing a large volume of tissue to isolate and concentrate the inorganic particles; HTA = high temperature ashing; LTA = low temperature ashing; KOH, bleach, Soluene = chemicals for digestion of tissue to remove organic matrix; acid = use of dilute acid to dissolve the nonsilicate portion of the ash; centr = centrifugation to isolate particles from suspension, filt = membrane filtration to remove particles from suspension usually prior to TEM grid preparation; c-coat, wick = preparation of a TEM grid by dissolving a piece of carbon-coated membrane filter by solvent wicking action to leave the particles embedded in the carbon film suspended on the grid; drop = preparation of TEM grid by evaporation of a small drop of a particle suspension on a carbon-coated TEM grid.

[d] Samples were pooled as an exposure group (32 subjects exposed to amphibole fibers in drinking water) and a control group (no amphibole fibers in drinking water).

[e] Number of fibers in urine exceeded number in blank for each urine sample.

[f] Amphibole concentrations in replicate preparations of tissues were found to fit a dose-response relationship with concentrations greatest in kidney and very low in muscle tissue.

[g] Some fibers were found in tissues (no comparison to blank samples) but concluded to be insignificant on the basis of a lack of preferential retention in any specific tissue, particularly the mesenteric lymphatic tissues. The authors also indicated difficulty in identifying fine fibers (<0.1 μm diameter) with the SEM.

TEM = Transmission Electron Microscopy

SEM = Scanning Electron Microscopy

OM = Optical Microscopy

evidence of penetration by ingested particles other than asbestos (mineral or synthetic fibers), thus demonstrating the possibility of such movement and subsequent tissue accumulation.

LeFevre et al. (1978) observed that mice, after drinking water suspensions of 2 μm diameter latex spheres for 2 months, had the latex particles accumulated in macrophages in intestinal Peyer's patches. Latex particles of 0.22 μm were reported by Sanders and Ashworth (1960) to migrate from the stomachs of rats to lymphatics of the mucosa, as well as to the liver and kidney tissues. Much larger particles of silica, in the form of opal phytoliths from plants, have been observed in digested mesenteric lymph node and kidney tissue from sheep that eat cereal chaff and grains (Nottle, 1977).

Volkheimer (1972) observed that particles of micrometer proportions are regularly incorporated in the GI tract by persorption. During persorption, corpuscular particles are passed between epithelial cells into the subepithelial layer where they are transported by portal circulation or chyle. Volkheimer (1974) later investigated the process of persorption in rats, rabbits, chickens, guinea pigs, dogs and pigs. Animals were administered suspensions of particulates by intragastric or rectal tube to determine the mechanisms of persorption. These particulates included starch granules, cellulose particles, powdered rabbit hair, charcoal, pollen, spores, polyvinyl globules and silicates. Animals were sacrificed at various times (not specified) after particulate administration. Upon histological examination of the small intestine, particles were found between epithelial cells, in the subepithelial layer of the mucosa and in the lumen of the lymph vessels. Two hours after dogs were given the particulate suspension, persorbed particles were found in body fluids (specific type not reported), chyle (from the thoracic duct), blood, bile and urinary bladder. The majority of the particles that were persorbed ranged between 15 and 75 μm in diameter. A silicate of 150 μm was reportedly found in the lymph of one animal. Volkheimer (1974) did not specify, however, the number of animals per species used in the study, the precise time of sacrifice following exposure, whether or not control animals were used, or how the particulates were identified in the histological samples. The concentration and volume of the particulate suspension were also not reported by the author. Despite these shortcomings, the study does provide some information as to the mechanism of persorption and the distribution of persorbed particles.

Schreiber (1974) reported that dyed cellulose fibers, administered orally in the form of specially stained plant food, were found in both the blood and urine of human subjects. The cellulose fibers were present in the urine for several weeks after ingestion.

These data on nonasbestiform minerals support the weight of evidence in Table III-1 that a number of particle/fiber types show evidence of GI migration in laboratory animal species and humans. Cook (1983) noted that based on the studies summarized in Table III-1 it would be difficult to conclude that asbestos fibers do not cross the GI barrier. The weight of evidence is, by far, in favor of the occurrence of this event. However, as Cook (1983) points out, it is perhaps more important to consider the fraction of ingested fibers that may be involved in GI migration rather than the probability of the migration actually occurring. Unfortunately, little information is available to estimate the percentage of fibers involved in actual migration. Sebastien et al. (1980) estimated that a maximum of 10^{-4} to 10^{-7} times the number of UICC chrysotile A fibers (mean

26.7×10^{10} f) or UICC crocidolite fibers (mean 13.7×10^{10} f) introduced to the stomach appeared in the lymph fluid of rats. Analyzing human urine, Cook and Olson (1979) detected $\sim 10^{-3}$ of the concentration present in the subject's drinking water (Lake Superior amosite: mean L = 1.42 μm; mean D = 0.20 μm, #fNR) that had been consumed ≤ 20 years before the study. Unfortunately, these data are limited in that neither the lymph fluid nor the urine can account for all fibers that may move across the GI mucosa. However, the data do indicate that a small percentage of fibers ingested are actually involved in penetration and consequently in tissue accumulation and increased cancer risk (Cook, 1983).

Injection of Asbestos. The applicability of injection experiments to human risk assessment has been viewed with skepticism. Such injections do simulate one potential human exposure condition (i.e., small amounts found in drugs in countries that permit the filtering of drugs through asbestos pads during production processes). However, the primary value is that injection of asbestos permits more controlled conditions than are possible in ingestion or inhalation experiments. Thus, these studies should not be disregarded solely on the basis of route of exposure.

Cunningham and Pontefract (1973) detected fibers in beverages (beer, wine and soft drinks) and were interested in determining if such fibers consumed orally can pass through the intestinal wall and enter the bloodstream. A stock solution was made to contain Quebec chrysotile (Johns Manville 7RF02) fibers the same length as those found in beverages (L = 0.5-2 μm; diameter NR) and determined to contain 9.4×10^{6} fibers/ℓ. An aliquot (assumed to be 350 mℓ) was then administered intragastrically to rats (number, species and sex not known). Asbestos fibers were found to accumulate in the omentum surrounding the small intestine, brain and lungs. According to the authors, counts could not be made on the liver and kidney sections.

Roe et al. (1967) injected 20 female CBA mice subcutaneously in two sites. Each injection contained 10 mg fiber suspended in 0.4 mℓ saline. Each animal received three injections into each flank. The flank was chosen as a site well distant from the thorax. Three fiber types (all South African) -- crocidolite (50% 0.5-2 µm in length, diameter NR, #fNR), amosite (56% 0.5-2 µm in length, diameter NR, #fNR) and chrysotile (DNR, #fNR) (Harrington, 1965) -- were tested. Crocidolite and amosite were solvent extracted to remove carcinogenic natural and contaminating oils. All three injected fiber types were found in the submesothelial tissues of the thorax and abdomen. In addition, extensive inflammatory changes and some sarcomas developed at the injection sites. Transport of fibers to submesothelial tissues culminated in mesothelioma.

Chrysotile (type NR, DNR, #fNR) injected intraperitoneally into rats was found to migrate into the peribronchial and perivascular tissues of the lung and was observed in alveolar epithelial cells (Karacharova et al., 1969). In another study using i.p. injection as the mode of exposure, UICC standard amosite (mean L = 3 µm, mean diameter NR, #fNR), anthophyllite (DNR, #fNR) or crocidolite (mean L = 3 µm, mean diameter NR, #fNR) was administered to female Wistar rats as a regimen of 20 mg/week for 5 weeks (Friedrichs et al., 1971). The animals were sacrificed 4 months after the initial injection and subjected to histological examination. Fibers of varying lengths were observed in abdominal granulomas, the shorter fibers being generally intracellular and the longer fibers extracellular. Transport of fibers from the site of injection was found to be somewhat dependent upon fiber length; shorter fibers are noted to be more readily transported than longer ones.

Kanazawa et al. (1970) investigated the migration of UICC crocidolite fibers (model L = 1.2 µm, diameter NR, #fNR) in mice following s.c. injection. Improved staining, microincineration and electron microscopy techniques led to a confirmation of lymphatic transport but demonstrated that the amount transported was less than formerly believed. Fibers accumulated in lymphoid tissues (primarily axillary lymph nodes) but were also concentrated in inguinal, mediastinal and lumbar nodes. Some fibers were found in the spleen and in nonlymphoid organs such as the liver, kidneys and brain, suggesting that fibers had also entered the bloodstream. Most asbestos fibers probably travel inside macrophages, although some larger fibers may be free in the lymph or blood (Kanazawa et al., 1970). Selective transport of fibers to the submesothelial tissue, as suggested in Roe et al. (1967), was not supported by this study.

The transport of Quebec (Johns Manville 7RF02) chrysotile fibers (L = 0.2-2.0 µm, diameter NR) from the maternal blood across the placenta to the fetus was reported by Cunningham and Pontefract (1974). Dosages of 1-3 mg (1 mg/mℓ of water) were injected into the femoral vein of female Wistar rats at 2-day intervals from days 10-14 of gestation. Total dose varied from 4-12 mg (4-12x10^5 f) of asbestos. The fetuses were removed by Caesarean section the day before parturition in a manner that prevented cross-contamination from the mother; the livers and lungs were then analyzed by electron microscopy. The presence of asbestos fibers in the fetus was highly variable. The livers and lungs analyzed were selected at random and thus, could have come from different fetuses in the same uterus. In the first experiment, the highest number of fibers found in fetal liver and lungs came from a dam administered four 3 mg injections (total dose = 12 mg or 12×10^5 f). Numbers of fibers found in liver and lungs were 27.03×10^6 f/g and 139.97×10^6 f/g, respectively. In a second experiment, with additional controls, the highest number of fibers found in fetal liver and lungs came from a dam administered five 2 mg injections (total dose = 10 mg or 10×10^5 f). Numbers of fibers found in the liver and lungs were 100.12×10^6 f/g and 2.90×10^6 f/g, respectively.

Interspecies Variability of Response to Asbestos. Zaidi (1974) emphasized the need for investigators to use suitable animal models to correlate results with effects in humans. He cited major differences between the stomachs of rats and humans as an example and suggested that the dog or the guinea pig would be a more suitable model. Zaidi (1974) discussed the possible role of the mucous barrier in preventing absorption of asbestos in the GI tract, and noted that high levels of mucous production, either as a species-specific phenomenon or as a result of individual differences in feeding, could influence the results in studies of uptake. It was suggested that destruction of the mucous barrier (e.g., by the use of drugs) might allow greater absorption of asbestos from the GI tract, leading to a greater neoplastic response.

Bioaccumulation/Retention

Patel-Mandlik and Millette (1983a,b) designed a study to determine if penetration, migration and retention occur in animals chronically exposed to ingested asbestos. Sprague-Dawley rats, previously exposed to chrysotile asbestos fibers *in utero*, were given 50 mg/kg intermediate range (IR) Environmental Health Sciences Sample No. 109C chrysotile asbestos (65% f >10 µm in length, diameter NR, #fNR) by gavage 2 times/week. This was done until natural death or sacrifice. The authors did not investigate whether death was related to asbestos exposure (e.g., death from tumor formation). The rats were then divided into groups by age at death: 0-200, 200-400, 400-600 and 600-800 days. Random samples (5/group) were taken and kidneys were analyzed for asbestos fibers. Four (1/age group) control rats (previously exposed _in utero_) were chosen to represent asbestos levels in control tissues. Fibers were shown to pass across the GI wall. In addition, a rise in fiber levels was detected in tissues from group 1 to group 3. However, levels dropped in group 4. The authors state that this drop could be due to time-related biological causes of low fiber recovery such as degradation of fibers beyond TEM identity and elimination of fibers in feces and urine. Thus, accumulation was demonstrated.

Metabolism

Little information is available on the metabolism of ingested asbestos. As noted in the Section on Absorption and Distribution, fiber penetration into and migration across the gut wall occurs. Seshan (1983) demonstrated that physical and chemical properties of UICC (DNR), NIEHS intermediate (DNR) or Globe, AZ fine (DNR) chrysotile change substantially with <1-hour exposure to simulated gastric juice (pH=1.2). The Zeta potential was changed from positive to negative; Mg++ ions were leached from the fibers; and the refractive index of the fiber decreased making the fiber more difficult to detect with a light microscope. When chrysotile (type not specified) was treated with 1N HCl, long range structural order was lost with a concomitant reduction in X-ray diffraction signal. For all three types of chrysotile treated with 1N HCl, the percent of fibers identifiable by electron diffraction was decreased after 30 minutes. Surface properties were altered with N_2 adsorption being doubled for NIEHS intermediate chrysotile treated for 2 hours but not for Globe, AZ fine chrysotile. Dye adsorption greatly increased for Globe, AZ fine chrysotile. No changes in X-ray diffraction signal were seen with crocidolite (type NR, DNR) exposed to 1N HCl. No information was reported on any change in the length and diameter of any of the treated fibers.

Lukens (1978a,b) performed immunochemical studies aimed at development of a method for determination of asbestos in environmental samples. His results indicated that, unlike normal control globulins, experimental globulins obtained from rabbits injected with bovine serum albumin-coated asbestos (Duke Standards Chrysotile, DNR) were found to bind with this same type of asbestos.

Elimination

As discussed in the Section on Absorption and Distribution, recent studies have resulted in contradictory conclusions regarding recovery of ingested asbestos fibers in urine of exposed test animals. Hallenbeck and Patel-Mandlik (1979) indicated that UICC Canadian chrysotile fibers (DNR, 3×10^{13} f) orally administered to baboons may be recovered in the urine.

Cook and Olson (1979) conducted a study in which human urine sediment, examined by transmission electron microscopy, contained amphibole fibers that the authors contend were clearly associated with the type of drinking water ingested by the subjects. Urine samples were obtained from residents of Duluth, MN drinking unfiltered water from Lake Superior (amosite: mean L = 1.42 μm; mean D = 0.20 μm; $5\text{-}800\times10^{7}$ f/L). The subjects reported no occupational exposure to asbestos. Ingestion of filtered water by two of these subjects resulted in a significant reduction of amphibole fibers in urine. Cook and Olson (1979) report that their data provide the first direct evidence for the passage of mineral fibers through the human GI mucosa.

Boatman et al. (1983) analyzed human urine samples for asbestos fibers. Seven residents of Everett, Washington where tap water contained $\sim200\times10^6$ f/ℓ (chrysotile) donated early morning urine samples over a 21-month period. The donors resided in the area <3 years (n=3) or >20 years (n=4) and reported no occupational exposure to asbestos. Four control donors resided in an area where the fiber content of the tap water was 100 times less than that of the test community. The fiber content of the urine of the <3-year residents was significantly lower ($p<0.05$) from the fiber content of the urine of the >20-year residents. This may be attributed to a high fiber content in the urine of one >20-year resident. The test group as a whole did not differ significantly from the controls with regard to urine fiber content. The authors recognize some problems associated with the study (e.g., fiber contamination of control water samples and, difficulties associated with the estimation of fibers in urine by use of present techniques). Yet, the numbers of fibers in the urines would have to increase at least 10-fold in order to obtain a convincing difference. Such a difference would probably not be accounted for by the problems of measurement. Thus, the authors state that even though the data are inconclusive, they suggest no relationship between high concentrations of fibers in drinking water and the numbers estimated for voided urine.

Summary

An important factor to consider when discussing the health risks associated with exposure to asbestos in drinking water is whether the fibers can penetrate the GI mucosa and thus reside in tissue. The weight of evidence is in favor of the occurrence of this event. However, the percentage of fibers shown to actually penetrate is small considering the total amounts ingested. Nevertheless, if penetration occurs only to a limited extent, tissue accumulation may be a factor in increased cancer risk from the ingestion of asbestos fibers.

Little is known about the metabolism of ingested fibers and there is no available information on the bioaccumulation/retention of ingested asbestos fibers. Simulated gastric juice has been demonstrated to alter the physical and chemical properties of chrysotile fibers and to a lesser extent, crocidolite fibers. One study on humans provides evidence that asbestos fibers pass through the GI mucosa and appear in the urine; another study on humans is inconclusive but suggests no relationship between the ingestion of fibers from drinking water and the elimination of fibers in urine.

IV. HUMAN EXPOSURE

This chapter will be submitted by the Science and Technology Branch, Criteria and Standards Division, Office of Drinking Water.

IV. SOURCES OF HUMAN EXPOSURE - ASBESTOS

Humans may be exposed to asbestos in drinking water, food, and air. Detailed information concerning the occurrence of and exposure to asbestos in the environment is presented in a draft document entitled "Estimated National Occurrence and Exposure to Asbestos in Public Drinking Water Supplies" (SAIC 1986). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food, and air.

Exposure Estimation

This analysis is limited to drinking water, food, and air, because these media are considered to be general sources common to all individuals. Some individuals may be exposed to asbestos from sources other than the three considered here. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats, and physiological characteristics related to age, sex, and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

A. DRINKING WATER

The contamination of drinking water by asbestos fiber occurs from the natural source of mineral erosion and from several anthropogenic sources. The natural surface of water erosion of asbestos minerals occurs predominantly in the states of California, Kentucky, Washington, Minnesota, Massachusetts and Georgia. The degree of such contamination is enhanced during the period of high runoff and river flow (Logsdon 1979). Geographically, there are several areas in the U.S. that are known or suspected to contain mineral deposits having high asbestos content, and such deposits occur predominantly in California, Alaska, Minnesota, Georgia, North Carolina and Vermont (SRI 1978).

The principal anthropogenic sources of asbestos in drinking water area: (1) A/C (asbestos cement) pipes employed in the distribution of drinking water, (2) mineral mining processes, (3) industrial discharges from facilities storing or processing asbestos, and (4) others, which includes the erosion of asbestos waste piles, the erosion of A/C tile roofings, and A/C pipe tappings.

For the development of standards on asbestos, emphasis is made to determine the occurrence of long fibers, >10 u, and high concentrations, >7.1 MFL.

ASBESTOS FIBER CONCENTRATION >5 MFL IN FINISHED WATER AND DISTRIBUTION DRINKING WATER .

The maximum (M) and average (A) asbestos fiber concentration for each city and the probable source of contamination if known are listed in Table 1 based on the studies of Millette et al (1979). The asbestos contamination of ground water in the San Luis Obispo (Calif.) area appears to be due to the asbestos contamination of the surface water reservoir which recharges it (Hayward 1984). A measured asbestos fiber concentration of 3,100 mgL in the reservoir is probably primarily due to the erosion of natural mineral outcroppings (Hayward 1984).

Asbestos fiber concentrations exceeding 5 mfL in Lakeland (Florida), Pensacola (Florida), Kentucky Dam Village (Kentucky), Paint (Pennsylvania), and Bishopville (South Carolina) appear to be related to asbestos pipe deterioration (Millette et al. 1979). Millette et al (1979) indicate that A/C pipe tapping is probably responsible for the reported asbestos fiber concentration of 10.2 MFL in a sample of Farmington distribution water since asbestos fiber concentrations in subsequent samples were well below 1 MFL. The high asbestos fiber concentrations in the distribution waters of Pensacola have been primarily attributed to A/C pipe deterioration (Millette et al. 1979; Buelow et al. 1980). However, only four of the

Table 1. ASBESTOS FIBER CONCENTRATIONS REPORTED TO EXCEED 5 mfL IN FINISHED DISTRIBUTION WATER OF GROUND WATER OR UNSPECIFIED ORIGIN

State	Location	Type of water	Source of water	No. of samples	Average miles of A/C pipe	Year	Total concentration (mfL)	Probable major cause
CA	San Luis Obispo	F	G	7	0.0	82	170M 93.3A	Mineral erosion
CT	Farmington	D	U	3	1.00		10.2M	A/C pipe tapping
FL	Lakeland	D	G	11	U	78	17.0M 4.09A	A/C pipe deterioration by H_2S
FL	Pensacola (combined)	D	G	36	1.03 (13)	75-79	33.0M 1.94A	A/C pipe deterioration or A/C pipe tapping
	Pensacola (Chantilly)	D	G	9	2.20 (5)	75-79	33.0M 4.52A	A/C pipe deterioration or A/C pipe tapping
	Pensacola (miscellaneous)	D	G	21	U	75-77	11.7M 1.36A	A/C pipe deterioration or A/C pipe tapping
KY	Kentucky Dam Village	D	U	1	U	78	48.5	A/C pipe deterioration
NM	Algodones	F	G	1	0.0	76	710	Unknown
PA	Paint	D	U	5	1.00 (1)	76,78	19.0M 8.01A	A/C pipe deterioration
SC	Bishopville	D	G	4	U	78	547M 262A	A/C pipe deterioration

F = finished water; D = distribution water; G = ground water; U = unspecified; M = maximum; A = average.

exceeding 2 MFL and only two of those four had concentrations exceeding 5 MFL. Therefore, since reports of high asbestos fiber concentrations in the distribution waters of Pensacola are somewhat isolated, additional factors such as A/C pipe tapping may be involved.

SIZE DISTRIBUTION OF ASBESTOS FIBERS IN DRINKING WATER

The size distribution of asbestos fibers in drinking water appears to depend to some extent on the source of the fibers (Craun et al. 1977; Tarter 1979; Buelow et al. 1980; Millette et al. 1980). Those studies indicate that substantially higher percentages of asbestos fibers from A/C pipe have lengths greater than 5 u and aspect (length/width) ratios greater than 100 u than do asbestos fibers originating from the erosion of natural mineral outcroppings.

Table 2 shows the size distribution of asbestos fibers from different sources in drinking water samples. It can be seen from Table 2 that approximately 16% and 21% of asbestos fibers in samples of drinking water which had passed through A/C pipe in Florida and South Carolina, respectively, had lengths greater than 5 u. By comparison, 0 and 2.5% of asbestos fibers from mineral erosion in samples of a Washington reservoir and a California raw water had lengths greater than 5 u. Similar results were reported by Craun et al. (1977) who compared the size distribution of asbestos fibers in of natural mineral outcroppings. An attempt is made to compare cumulative fiber length data on water quality before and after transport through the asbestos cement pipe. For any given fiber length, the cumulative plot gives the estimated fraction of fibers with smaller lengths. As shown in Figure 1, this analysis indicates that after the transport in the A/C pipe, there is a decrease in the percentage of fibers with lengths less than any given length between 0.1 and 10 and a corresponding increase in the fiber size distribution.

Tarter (1979) also studied the effect of water treatment on the size distribution of asbestos fibers in drinking water. Figure 2 is a comparison of the cumulative plots of fiber length data for water before (T) and after (X) passing through the San Andreas water treatment plant. The treatment at the San Andreas water treatment plant includes coagulation, filtration flocculation, caustic soda, fluoridation, and chlorination. However, even though the treatment plant is fairly effective in reducing asbestos fiber concentrations, it surprisingly does not appear to have any significant effect on the size distribution of the fibers as can be seen from Figure 2.

As previously discussed, the proportion of asbestos fibers with lengths greater than 5 u appears to be much higher for fibers originating from A/C pipe than for fibers originating from the erosion of natural mineral outcroppings. Data from Stewart et al. (1976) indicates that the proportion

Figure 1. CUMULATIVE PLOTS OF POOLED FIBER LENGTH DATA BEFORE (T) AND AFTER (X) TRANSPORT THROUGH A/C PIPE

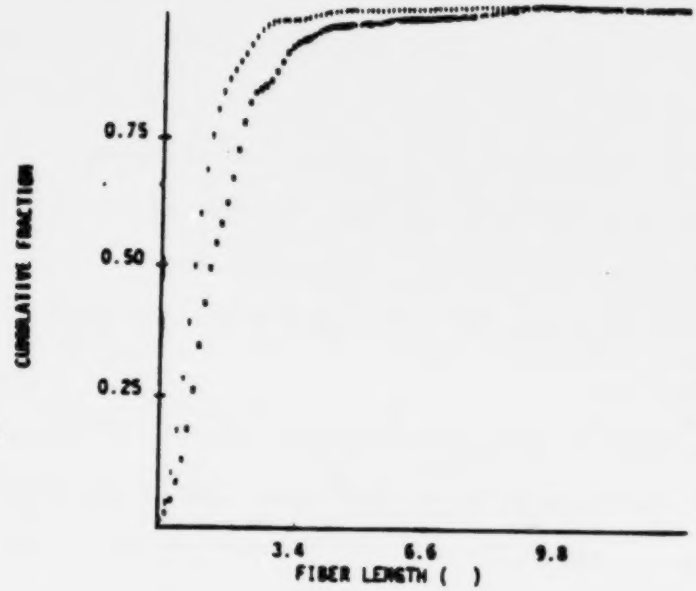
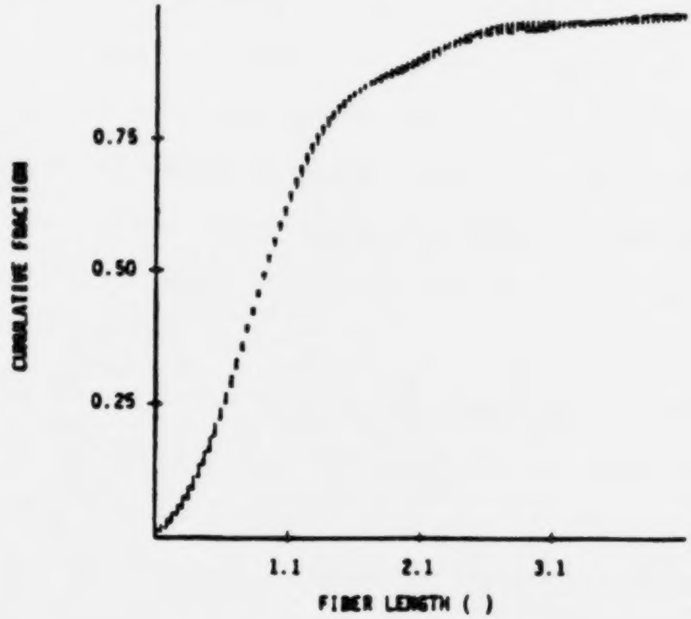


Figure 2. CUMULATIVE PLOTS OF FIBER LENGTH DATA BEFORE (T) AND AFTER (X) WATER TREATMENT



of asbestos fibers with lengths greater than 5 u is also much higher for asbestos fibers in manufacturing effluents than for fibers from mineral erosion. The occurrence document lists the concentration of asbestos fibers in effluents from various asbestos product manufacturers and the percentage (in parentheses) of the fibers with lengths greater than 5 u. It is also indicated that generally greater than 10% and occasionally greater than 40% of the asbestos fibers in manufacturing effluents exceed 5 u in fibre length. There is no evidence of any widespread contamination of drinking water by manufacturing effluents. However, the data reported by Stewart et al. (1976) indicates that any such contamination could potentially introduce high proportions of asbestos fibers with lengths greater than 5 u into drinking water.

The distribution of asbestos fiber aspect ratios in drinking water appears to also be dependent upon the source of the fibers, and somewhat parallels the size distribution. Table 3 **shows the aspect** ratio distribution of asbestos fibers **from different** sources in drinking water. It can be seen from Table 3 that approximately 19% and 20% of asbestos fibers in samples of drinking water which had passed through A/C pipes in Florida and South Carolina, respectively, had aspect ratios greater than 100 - <500. In comparison, 0% and 4% of asbestos fibers from mineral erosion in samples of a Washington reservoir and a California raw water had aspect ratios greater than or equal to 100 .

Table 3. DISTRIBUTION OF FIBER ASPECT RATIOS IN VARIOUS WATER SUPPLIES

	Number of fibers	% distribution of fiber aspect ratios				
		3-<5	5-<10	10-<100	100-<500	≥500
Reservoir water (WA)	210	1	7.4	91.6	0	0
Raw water (CA)	240	2	6	89	4	0
Asbestos cement pipe system (FL)	503	1	3	76	19	1
Asbestos cement pipe system (SC)	215	6	3.5	67	20	3.5
Cistern (VI)	342	1	16	77	5	1

Source: Millette et al. 1980

POPULATION EXPOSURE ESTIMATION

National population exposure estimates of asbestos fiber concentrations exceeding 7.1 MFL, and also having fiber lengths longer than 10 microns, are listed in Table 4.

There are very limited data available for characterizing human intake of asbestos from drinking water provided by public water supplies. Upon combining all of the available data from more then 400 cities having drinking water concentration of asbestos fibers of all lengths with the limited available fiber length distribution data to estimate the numbers of people nationwide who are exposed to concentrations of asbestos

Table 4. CHARACTERISTICS OF U.S. DRINKING WATER SUPPLY SYSTEMS CORRESPONDING TO SPECIFIC EXPOSURE TO ASBESTOS FIBER LENGTH >10 u, CONCENTRATION >7.1 mFL AND AT RISK >10 OF CONTINUOUS EXPOSURE, 2 L/d.

System type	U.S. systems total	Number of people served (millions)	A/C pipe used	% systems with fiber >10 u	Number systems having exposure risk 10^{-6} >7.1 mFL >10 u	Number people receiving exposure risk 10^{-6} >7.1 mFL >10 u
Ground Water	18,126	7 - 21	Yes	11%	562	7×10^4
	19,573	49 - 73	No	0.5%	0	0
Surface Water (CA&WA) exclu	3,257	7 - 21	Yes	11%	21	6.7×10^4
	6,903	97 - 120	No	11%	26	1×10^4
Surface Water (CA&WA) only	1,143	4 - 12	Yes	2%	0	0
	273	6 - 14	No	0.5%	0	0

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fibers (exceeding 10 u in length) >71, >7.1, >0.71, >0.071, and >0.0071 million fibers per liter (mfL) corresponding to estimated carcinogenic risks of $>10^{-5}$, $>10^{-6}$, $>10^{-7}$, $<10^{-8}$, and $>10^{-8}$, respectively. The estimated number of people exposed to the concentration of asbestos fibers corresponding to a lifetime carcinogenic risk of 10^{-6} ranges between 730,000 and 1,200,000. Of these, between 220,000 and 650,000 are using ground water and between 510,000 and 580,000 are using surface water.

B. DIET

Limited quantitative information is available on the contribution of food products to the total asbestos exposure of the U.S. population. Asbestos contamination of foods may occur directly due to the release of asbestos fibers into the food from filters used to purify the product (USEPA 1980), or indirectly from the erosion of asbestiform minerals used in the building materials of the food industry (Huff 1978, as cited in Rowe 1983).

Rowe (1983) indicated that dietary materials,that have been reported to contain or likely to contain asbestos,occur among foods,such as,vegetable oil, lard, mayonnaise, ketchup, and meats (Merliss 1971; Wolff and Oehume 1974; Albright et al. 1979, all cited in Rowe 1983); and beverages such as beers, sherries, ports, vermouth, and soft drinks (Biles and Emerson

1968; Cunningham and Pontefract 1973; Wehman and Plantholt 1974, all cited in Rowe 1983). Table 5 summarizes the levels of asbestos in the beverages mentioned above. It is not known whether the source of the asbestos in beverages could be the drinking water from which the drinks were made or the filtration process used by the food industry.

No information was available from the Food and Drug Administration (FDA) on the occurrence of asbestos in food.

Table 5. CONCENTRATION OF ASBESTOS IN BEVERAGES

substance	No. of observations	Concentration, million fibers/L[a]
Beer	4	1.1 - 6.6
Sherry	3	2 - 2.6
Port	1	2.1
Vermouth	2	1.8 - 11.7
Soft drinks	4	1.7 - 12.2

[a] Analyzed by electron microscopy.

Source: USEPA 1982, as cited in Rowe 1983

Rowe (1983) estimated that the daily intake of asbestos from a 12-ounce can of beer was 2.4×10^6 EM fibers; the daily intake from 3 ounces of talc-coated rice ranged from 7.8×10^9 to 3.1×10^{11} fibers.

C. AIR

Limited information was obtained on the presence of asbestos in ambient air. Information on the typical size of airborne asbestos fibers is not well documented. Nicholson (1978, as cited in Rowe 1983) reported that asbestos fibers in ambient air tend to be very small; some fibers are up to 1 um in length while most fibers are approximately 0.1 um in length and have a diameter between 0.02 and 0.05 um. More recently, however, Nicholson has stated that, based on monitoring practices in Germany, asbestos fibers from environmental exposures are more equivalent to those from occupational exposures (Rowe 1983).

The U.S. Environmental Protection Agency (EPA) reported a study of asbestos concentration in 187 quarterly composite samples from 48 U.S. cities collected from 1969-1970. The study showed that chrysotile asbestos was present in essentially all of the cities sampled (Nicholson 1971; Nicholson and Pundsack 1973, as cited in USEPA 1980). In the study, 98.5% of the samples contained concentrations of asbestos below 20 ng/m^3, and 100% of the samples contained levels below 100 ng/m^3. Nicholson (1971, as cited in NRC 1984) reported a median value for this study of 1.6 ng/m^3. Of three samples that contained concentrations of asbestos greater than 20 ng/m^3, one was from a city that had a major shipyard and another was from a city that had four brake manufacturers. Therefore, the samples could include a contribution from these specific sources in addition to the concentration in the ambient air (USEPA 1980).

USEPA (1974, as cited in NRC 1984) reported a median concentration of 2.3 ng/m^3 for 127 samples from various U.S. cities. In that study, 98.5% of the samples contained levels of asbestos below 20 ng/m^3, while 100% of the samples contained levels below 50 ng/m^3 (USEPA 1974, as cited in USEPA 1980).

In a study of ambient air in New York City, Nicholson et al. (1971, as cited in USEPA 1980) collected samples in the five boroughs of New York (Manhattan, Brooklyn, Bronx, Queens, Staten Island). Samples were taken during daytime working hours and, due to construction and automobile activities, concentrations may have been higher compared to nighttime periods. Of the 22 samples taken in the five boroughs, a range of 2 to 65 ng/m^3 was reported, with an overall average of 17.4 ng/m^3. Nicholson et al. (1971, as cited in NRC 1984) reported a median concentration of 13.7 ng/m^3 for this study.

Nicholson et al. (1971, as cited in USEPA 1980) also conducted a study in lower Manhattan near sites where spraying of asbestos-containing fireproofing material was taking place. The study was to determine if such activity contributed to elevated asbestos levels. The results proved that the spraying did increase the air concentrations of asbestos as chrysotile fibers in 22 samples ranged from 3.5 to 375 ng/m^3, with an overall average concentration of 40.9 ng/m^3. Nicholson et al. (1971, as cited in NRC 1984) reported a median concentration of 22.5 ng/m^3 for this study.

Nicholson et al. (1975, as cited in USEPA 1980) reported variations in the average concentration of chrysotile asbestos fibers near 19 buildings at "outside air" sites (primarily office buildings) in 5 cities from 0 to 48 ng/m^3. The number of samples, as well as the number of sites and their location, were not reported.

Suta and Levine (1979), as cited in NRC 1984) estimated that the rural U.S. population (approximately 60 million people) was exposed to concentrations of asbestos from 0.01 to 0.1 ng/m^3. In contrast, they estimated that the urban U.S. population (approximately 170 million people) were exposed to concentrations of asbestos greater than 1 ng/m^3.

Thompson (1978, as cited in NRC 1984) examined 20 samples obtained downwind from an emission source (location unknown) and found average asbestos fiber concentrations ranging from 0.03 to 8,200 ng/m^3. Thompson also investigated various industrial cities in the U.S., and found ranges of concentrations for the samples analyzed of 0.6 to 95.0 ng/m^3 in 1969-1970 (number of samples not given) and 0.4 to 27.7 ng/m_3 in 1971-1972.

Several airborne asbestos concentrations near industrial sites were reported in Rowe (1983). The ambient air concentrations near the Union Carbide mill and waste pile in King City, California and near the Johns-Manville mill and water dump in Coalinga, California were 1.03 million fibers/m^3 and and 593 million fibers/m^3, respectively (USEPA 1982, cited in Rowe 1983).

Asbestos fibers are released to air during all stages of the life cycle of asbestos products. Asbestos products include building materials, such as roofing materials and insulation, break liner, insulation, and asbestos cement products. Asbestos fibers are persistent in the environment and can easily be transplanted great distances from their point of release. Atmospheric sampling programs conducted in remote rural areas of the United States and Germany have found asbestos fiber levels between 0.01 and 0.12 ng/m^3 (USEPA 1986). In areas of higher human population density, measured asbestos concentrations in the air are typically much greater. Surveys of urban areas report levels in the range of 1 to 5 ng/m^3 (USEPA 1987). One survey of New York city reported levels ranging from 265 ng/m^3. EPA has been concerned over the possible contribution of asbestos from tap water to indoor air. However, a recent survey of homes found only a small elevation of indoor air levels over ambient levels in homes with asbestos contaminated water (New York State Dept. of Health 1986).

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V. HEALTH EFFECTS IN ANIMALS

The fate of asbestos in animals, as well as the specific physiological, biochemical, metabolic or morphologic effects caused by its presence are dependent on the organism involved, the route of administration, the length [illegible] exposure, the quality of exposure, synergistic or antagonistic interactions with other substances and the physical characteristics of the form of asbestos involved. In this chapter, the various types of health effects associated with oral exposure to asbestiform minerals will be discussed.

Several recent studies have investigated the health effects of ingested asbestos fibers in animals. With the exception of one study, all work from 1977 to the present involves the detection of chronic health effects. The lack of acute effects studies appears not be be an omission but rather a consequence of the nature of health effects from exposure to asbestos by ingestion (i.e., oncogenesis).

General Toxicity

Effects Associated with Acute Exposure. Effects resulting from the acute exposure of animals to asbestos are summarized in Table V-1.

Ingestion Studies -- Jacobs et al. (1978a) fed 3-month-old male MRC hooded rats 0.5 mg or 50 mg (#fNR) of UICC Rhodesian chrysotile (DNR) daily for 1 week and subsequently examined the GI tract tissue by light and electron microscopy. No effects were noted in esophagus, stomach or cecum tissue, but structural changes in the ileum, particularly of the villi, were seen. Clumps of nuclei and mucinous material were present in the colon

TABLE V-1

General Toxicity of Asbestos

Species/ Test System	Sex	Route of Exposure	Types of Asbestos and Fiber Dimensions[a]	Dose	Duration	Health Effects	Reference
Acute Exposure							
Rat	M	ingestion	UICC Rhodesian chrysotile (DNR)	0.5 or 50 mg/day (#FNR)	1 week	Practically no effects detected in the esophagus, stomach or caecum, but more discrete changes seen in the colon, rectum and small intestine.	Jacobs et al., 1978a
Human embryonic intestine-derived (I-407) cells	NR	*In vitro*	7.2% chrysotile (DNR)	0.001-5.0 g/ℓ[b] 1 g/ℓ	3 days	The amosite sample was the most cytotoxic. The drinking water samples were 100-fold less toxic than amosite. The order of toxicity of the drinking water samples was San Francisco > Seattle > Duluth.	Reiss et al., 1980b
Macrophages	NA	*In vivo* and *In vitro*	NR	-		Review article of the effects of asbestos on macrophages.	Miller, 1978
Malignant mouse macrophage-like cell line P338D	NA	*In vitro*	crushed quarried serpentine rock	100 µg/ℓ	72 hours	The fibrous serpentine (asbestos) was cytotoxic, while the platy serpentine (groundrock) had no effect on cell growth.	Frank et al., 1979
Human blood lymphocytes	NA	*In vitro*	UICC Canadian chrysotile B (DNR)	400 µg/ℓ (#FNR)	72 hours	No cytotoxicity towards mononuclear cells was observed.	Kagamimori et al., 1980
Antibody-coated Chang cells	NA	*In vitro*	chrysotile	3 µg/mℓ or 5 µg/mℓ	20 hours	Antibody-dependent cell-mediated cytotoxicity was inhibited by the presence of chrysotile.	Kagamimori et al., 1980

TABLE V-1 (cont.)

Species/ Test System	Sex	Route of Exposure	Type of Asbestos and Fiber Dimensions	Dose	Duration	Health Effects	Reference
Chronic Exposure							
Rat	M	ingestion	UICC Rhodesian chrysotile/day(DNR)	0.5 or 50 mg (#/NR)	14 months	Greatest changes in the mucosal lining cells of the ileum. Practically no effects detected in the esophagus, stomach or caecum, but more discrete changes seen in the colon, rectum and small intestine.	Jacobs et al., 1978a

[a] Type of asbestos and dimensions (dimensions dependent on method of preparation):

	Modal Length (μm)	Modal Width (μm)
Crocidolite, UICC (South African)	0.6	0.13
Amosite, UICC (South African)	1.4	0.14
Tremolite (Montana) UICC	5.1	0.17
Anthrophyllite, UICC (Finnish) from Langer et al., 1974 (ultrasonically dispersed in water)	5.1	0.18
Chrysotile, NIEHS Short Range (SR), (Calif., Union Carbide)	0.66	0.059
Chrysotile NIEHS Intermediate Range (IR), (Quebec, Johns Manville-Plastobest-20) from NTP, 1985	0.82	0.089
	Range of Mean (μm)	Range of Mean (μm)
Chrysotile (Quebec) from Atkinson et al., 1971 (after milling)	1000-2000	0.030-0.038

[b] Samples contained serpentine and amphibole minerals

DNR - dimensions not reported

NA - not applicable

NR - Not reported

and rectum, though no morphological cellular changes were observed. The authors concluded that the observed changes were consistent with a mineral-induced cytotoxicity. In a subsequent report, Jacobs et al (1978b) found a significant increase in [^{3}H]-thymidine incorporation into DNA in the small intestinal mucosa, colon, rectum, spleen and stomach of rats following ingestion of 50 mg/day (#fNR) of UICC Rhodesian chrysotile (DNR) for 1 week and for 5-15 months. These results suggest that asbestos interferes with DNA metabolism in rat tissue. Finally, Jacobs and Richards (1980) demonstrated that asbestos may interfere with the active transport of glucose across the small intestine wall of a rat following 10 weeks of ingesting 50 mg (#fNR) chrysotile/day (DNR). The mean level of radiolabeled glucose was significantly lower in the chrysotile fed rats than in the controls.

A single oral dose of UICC Rhodesian chrysotile A (DNR, #fNR) to rats (3-8/dose) produced a subsequent increase in [^{3}H]-thymidine in the stomach (5 and 25 mg chrysotile/kg), duodenum (25 and 50 mg chrysotile/kg) and jejunum (5, 25, 50 and 100 mg chrysotile/kg) after 3 days (Amacher et al., 1975). The authors suggested that cellular proliferation and DNA synthesis may, therefore, be stimulated by chrysotile ingestion. In a study of asbestos carcinogenicity, Donham et al. (1980) noted a significant reduction in cyclic-AMP levels in the colons of asbestos-fed animals [milled UICC Canadian chrysotile B (DNR, #fNR)] compared with controls (see Other Effects, Carcinogenicity Section).

In Vivo and In Vitro Studies -- The effects of chrysotile asbestos UICC Canadian chrysotile B (DNR) on mononuclear cells in vitro were studied by Kagamimori et al. (1980). Human blood lymphocytes were cultured with

400 μg chrysotile/ℓ (#fNR) and observed after 24, 48 and 72 hours of incubation. Chrysotile asbestos was found not to be cytotoxic to these cells. In an antibody-dependent cell-mediated cytotoxicity experiment, the same investigators demonstrated that antibody-coated Chang cells and effector cells cultured with chrysotile (3 and 5 μg/mℓ) showed a significant decrease in the release of ^{51}Cr as compared with controls. The inhibition of the antibody-dependent cell-mediated cytotoxicity by chrysotile asbestos appeared to be due to the prevention of contact between antibody-coated target cells and effector cells.

Reiss et al. (1980b) assessed the toxicity of six asbestos-containing particulate samples of drinking water from locations throughout the United States. Human embryonic intestine epithelial cells (I-407) were used for the cytotoxicity assay. The assay was quantified by measuring the inhibition of the I-407 cell colony formation following exposure to 0.001-5 g/ℓ of each particulate sample. San Francisco drinking water samples containing 7.2% chrysotile (DNR) inhibited colony formation by 96% at a dose of 1 g/ℓ (#fNR). A Seattle drinking water concentration of 2.5 g/ℓ (#fNR) was found to inhibit 73% of colony formation. This sample was known to contain 2% chrysotile (DNR, #fNR). The drinking water sample from Duluth, which contained amphibole crystals (DNR), was found to be the least toxic of the drinking water samples with 88% cell colony inhibition occurring at a concentration of 5 g/ℓ (#fNR). Concentrations below those mentioned inhibited <50% of the cell colonies. The authors concluded that asbestos exerted its cytotoxicity through a specific physiochemical mechanism. They did not provide details of the specific nature of this mechanism.

Effects Associated with Chronic Exposure. There are few noncarcinogenic effects associated with the chronic ingestion of asbestos. Jacobs et al. (1978a) reported feeding 3-month-old male MRC hooded rats 0.5 or 50 mg (#fNR) UICC Rhodesian chrysotile (DNR) daily for 14 months. Rats fed 50 mg/day for 14 months had the greatest changes in the mucosal lining cells of the ileum; otherwise, the results were similar to those of the acute exposure studies (i.e., marked tissue changes in the ileum, clumps of nuclei and mucinous material present in the colon and rectum though no morphological changes, and practically no effects in the esophagus, stomach and caecum).

Detailed pathology examinations were conducted in the studies of the effects of ingesting Penge, Transvaal, Rep. South Africa amosite and chrysotile in hamsters and amosite in F344 rats by the National Toxicology Program (NTP, 1982a,b,c). No adverse effects on body weight or survival were reported. No nonmalignant effects were noted at a greater frequency than in control animals in any study. The details of these studies are discussed in the section on Carcinogenicity.

Target Organ Toxicity

No specific organ has been identified as a target organ following the ingestion of asbestos fibers. Changes were detected in the colon, rectum and small intestine and, to a greater extent, in the mucosal lining cells of the ileum following longer exposure durations. Cytotoxic effects have been demonstrated through *in vitro* testing procedures.

Other Effects

Carcinogenicity.

Oral Administration -- Condie (1983) reviewed the animal studies on ingested asbestos other than the large-scale feeding studies conducted by the NTP of the National Institute of Environmental Health Sciences (NIEHS). Table V-2, adapted from Condie (1983) summarizes the results of 12 oral studies.

Smith et al. (1965) reported results of feeding 45 hamsters 1% (#fNR) chrysotile (DNR) or amosite (DNR) in their diet. One neoplasm with no detectable asbestos was observed in the mesentary of the colon. However, the finding of fibers in tumor tissue would be unlikely and, as these tumors are rare in hamsters, this result cannot be totally dismissed. Webster (1974) reported that baboons (number not reported) exposed to "heavy" concentrations (dose not reported, #fNR) of asbestos (type not reported, DNR) in food and drinking water for ≤5 years did not develop any peritoneal or GI tumors. The 5-year observation time in this species is too short for any meaningful conclusions to be drawn from this experiment.

Wagner et al. (1977) fed groups of 32 Wistar SPF rats 100 mg/day Italian talc or UICC Canadian chrysotile in malted milk powder for 5 days/week for 100 days over a 6-month period. Controls (N=16) were fed malted milk. Mean lengths of survival from the start of feeding were 614 days, 619 days and 641 days for those given talc, crysotile and malted milk, respectively. One gastric leiomyosarcoma was observed in an animal fed talc and one was observed in an animal fed crysotile. None of these tumors occurred in the controls.

TABLE V-2

Summary of Asbestos Ingestion Carcinogenicity Studies[a]

Species	Type of Asbestos and Fiber Dimensions[a]	Dose/ Vehicle	Exposure Time	Study Duration	No. Animals	Tumors		Reference
					Initial/Examined	No.	Location Type[c]	
Hamster	chrysotile (DNR) amosite (DNR)	1% in diet (#FNR)	NR	NR	45/NR	1	Neoplasm in mesentary of the colon	Smith, et al., 1965
Baboons	NR (DNR)	NR, "heavy concentrations" (#FNR) in diet and drinking water	≤5 years	≤5 years	NR	0	NA	Webster, 1974
Rat	crocidolite	0.15% in diet ad lib	78 weeks	78 weeks	40/12	0	NA	Bonser and Clayson, 1967
	control	0	0	86 weeks	65/25	1	Liver-S	
Rat	chrysotile (DNR)	5% in diet (#FNR) ad lib	21 months	21 months	10/10	0	NA	Gross et al., 1974
	control	0	0	21 months	5/5	0	NA	
Rat	chrysotile (DNR)	10 mg/week in butter (#FNR)	16 weeks	1.5 years	31/31	2	Breast-C	Gross et al., 1974
	crocidolite (DNR)	5 mg/week in butter (#FNR)	16 weeks	1.5 years	33/33	0	NA	
	crocidolite (DNR)	10 mg/week in butter (#FNR)	16 weeks	1.5 years	34/34	1	Node-L	
	control	0	0	1.5 years	24/24	5	3 Breast-C, Thigh-S, Node-L	
Rat	crocidolite (DNR) (2 sources)	10 mg/week (#FNR) in butter	18 weeks	1.5 years	63/63	0	NA	Gross et al., 1974
	control	0	0	1.5 years	24/24	0	NA	
Rat	53% chrysotile (DNR) in filter material	20 mg/day (FNR) (50 mg/kg bw/day diet)	life	441 days[d]	50/42	12	Lung-C, 4 Kidney-C, 3 Node-L, 4 Liver-C	Gibel et al., 1976
	talc	20 mg/day (50 mg/kg bw/day diet)	life	649 days[d]	50/45	3	Liver-C	
	control	0	0	702 days[d]	50/49	2	Liver-C	

TABLE V-2 (cont.)

Species	Type of Asbestos and Fiber Dimensions[a]	Dose/ Vehicle	Exposure Time	Study Duration	No. Animals	Tumors		Reference
					Initial/Examined	No.	Location Type[c]	
Rat	chrysotile (DNR)	1% in feed with 5% corn oil (ØFNR) ad lib	24 months	24 months	10/7	6	Brain-S, Pituitary-C, Node-L, 2 Kidney-C Peritoneum-S	Cunningham et al., 1977
	control	0	0	24 months	10/8	1	Peritoneum-S	
Rat	chrysotile (DNR)	1% in feed with 5% corn oil (ØFNR) ad lib	24 months	30 months	40/36	11	2 Thyroid-C, Thyroid-S, Liver-C, Chemodectoma jugular body, Colon-C, Ileum-S, Adrenal-C, 2 Node-L, Bone-S	Cunningham et al., 1977
	control	0	0	30 months	40/32	11	Thyroid-C, Liver-C, 2 Adrenal-C, Kidney-C, Node-L, 5 Fat-S	
Hamster	amosite, UICC (DNR)	0.5 mg/ℓ in drinking water ad lib (ØFNR)	23 months	23 months	60/60	1	Lung-C	Smith et al., 1980
	amosite, UICC (DNR)	5 mg/ℓ in drinking water ad lib (ØFNR)	23 months	23 months	60/60	3	2 Stomach-C, Peritoneal Mesothelioma	
	amosite, UICC (DNR)	50 mg/ℓ in drinking water ad lib (ØFNR)	23 months	23 months	60/60	0	NA	
	taconite tailings (DNR)	0.5 mg/ℓ in drinking water ad lib (ØFNR)	23 months	23 months	60/60	1	Uterus-S	
	taconite tailings (DNR)	5 mg/ℓ in drinking water ad lib (ØFNR)	23 months	23 months	60/60	0	NA	
	taconite tailings (DNR)	50 mg/ℓ in drinking water ad lib (ØFNR)	23 months	23 months	60/60	0	NA	
	control	0	0	23 months	120/120	1	Node-L	

TABLE V-2 (cont.)

Species	Type of Asbestos and Fiber Dimensions[a]	Dose/ Vehicle	Exposure Time	Study Duration	No. Animals Initial/Examined	Tumors No.	Tumors Location Type[c]	Reference
Rat	chrysotile B, UICC Canadian (DNR)	10% in diet (#FNR) ad lib	32 months	32 months	240/189	4	3 Colon-C, Abdominal Mesothelioma	Bonham et al., 1980
	cellulose fiber	10% in diet ad lib	32 months	32 months	242/197	2	Colon-C	
	control	0	0	32 months	121/115	3	Colon-C	
Rat	azoxymethane[e]	7.4 mg/kg week s.c.	10 weeks	34 weeks	21/21	12	5 Ileum-C, 7 Colon-C	Ward et al., 1980
	azoxymethane plus amosite, UICC (DNR)	7.4 mg/kg week s.c. 10 mg, 3/week (#FNR) IG	10 weeks	34 weeks	21/18	10	3 Ileum-C, 7 Colon-C	
	azoxymethane plus chrysotile B, UICC (DNR)	7.4 mg/kg week s.c. 10 mg 3/week (#FNR) IG	10 weeks	34 weeks	21/21	10	4 Ileum-C, 6 Colon-C	
	amosite, UICC (DNR)	10 mg 3/week (#FNR) IG	10 weeks	34 weeks	21/21	0	NA	
	chrysotile B, UICC (DNR)	10 mg 3/week (#FNR) (#FNR) IG	10 weeks	34 weeks	21/21	0	NA	
	saline	1.0 mℓ 3/week IG (gavage)	10 weeks	34 weeks	21/21	0	NA	
	untreated	0	0	34 weeks	21/21	0	NA	
Rat	azoxymethane	7.4 mg/kg week s.c.	10 weeks	95 weeks	50/48	39	12 Ileum-C, 27 Colon-C	Ward et al., 1980
	azoxymethane plus amosite, UICC (DNR)	7.4 mg/kg week s.c. 10 mg 3/week (#FNR) IG	10 weeks	95 weeks	50/48	44	15 Ileum-C, 29 Colon-C	
	saline plus amosite UICC, (DNR)	1/week (s.c.) 10 mg 3/week (#FNR) IG	10 weeks	95 weeks	50/49	17	Ileum-C 16 Colon-C	

TABLE V-2 (cont.)

Species	Type of Asbestos and Fiber Dimensions^a	Dose/ Vehicle	Exposure Time	Study Duration	No. Animals	Tumors		Reference
					Initial/Examined	No.	Location Type^c	
Rat	filtered Duluth tap water	1 mfℓ^f in drinking water ad lib	690 days^d	690 days^d	28/27	3	Lung-C, Ovary-C Forestomach-C	Hilding et al., 1981
	unfiltered Duluth tap water	100 mfℓ in drinking water ad lib	960 days^d	960 days^d	30/28	4	Salivary Gland-C, Skin-C, Uterus-S, Mediastinum-L	
	Lake Superior 6% >5µm water sediment	5000 mfℓ in drinking water ad lib	840 days^d	840 days^d	22/22	3	Lung-C, Skin-C Uterus-S	
	taconite tailings	100,000 mfℓ in drinking water ad lib	870 days^d	870 days^d	30/30	3	Neck-S, Chest Wall-S, Mediastinum-L	
	chrysotile plus UICC amosite 6% >5µm	20 mg/day (0FNR) in cottage cheese	870 days^d	870 days^d	30/30	7	Breast-C, 2 Fibrous Histiocytoma, Skin-C Mediastinum-L, Pleural Mesothelioma	
	amosite UICC 6% >5µm	300 mg/day (0FNR) in cottage cheese	750 days^d	750 days^d	20/20	1	Leukemia	
	diatomaceous earth	20 mg/day in cottage cheese	840 days^d	840 days^d	30/30	5	Salivary Gland-C, Uterus-S, Skin-C, Peritoneal Mesothelioma	
Rat	amosite, UICC (DNR)	250 mg/week in margarine (0FNR)	25 months	life	24/24	1	Stomach-S	Bolton et al., 1982
	crocidolite, UICC (DNR)	250 mg/week in margarine (0FNR)	25 months	life	22/22	1	Adrenal-C	
	chrysotile, UICC (DNR)	250 mg/week in margarine (0FNR)	25 months	life	22/22	5	Fat-S, Pleural Histiocytoma, Adrenal-C, Plasma Cell Tumor	

TABLE V-2 (cont.)

Species	Type of Asbestos and Fiber Dimensions[a]	Dose/ Vehicle	Exposure Time	Study Duration	No. Animals	Tumors		Reference
					Initial/Examined	No.	Location Type[c]	
Rat	margarine control	0	0	life	24/24	4	Adrenal-C, Bladder-C, Peritoneum-S	Bolton et al., 1982
	control	0	0	life	23/23	2	Fat-S, Lymphoma	
Rat	chrysotile - IR median L - 0.82 μm median D - 0.089 μm	1% in diet (1291×10^6 f/g)	beginning with dams through lifetime	neonatal through lifetime	250/250	9	Benign epithelial neoplasms (adenomatous polyps) of the large intestine	NTP, 1985

[a] Source: Adapted from Condie, 1983 with additions

[b] Type of asbestos and dimensions (dimensions dependent on method of preparation):

	Modal Length (μm)	Modal Width (μm)
Crocidolite, UICC (South African)	0.6	0.13
Amosite, UICC (South African)	1.4	0.14
Tremolite (Montana) UICC	5.1	0.17
Anthrophyllite, UICC (Finnish) from Langer et al., 1974 (ultrasonically dispersed in water)	5.1	0.18
Chrysotile, NIEHS Short Range (SR), (Calif., Union Carbide)	0.66	0.059
Chrysotile NIEHS Intermediate Range (IR), (Quebec, Johns Manville-Plastobest-20) from NTP, 1985	0.82	0.089
	Range of Mean (μm)	Range of Mean (μm)
Chrysotile (Quebec) from Atkinson et al., 1971 (after milling)	1000-2000	0.030-0.038

[c] C - carcinoma; S - sarcoma; L - lymphoma

[d] Mean survival time

[e] Azoxymethane and saline given subcutaneously, amosite, chrysotile and saline administered by oral gavage

[f] mfl - Million amphibole fibers/liter

DNR - Dimensions not reported; #FNR - number of fibers not reported; IG - intragastric; NA - Not applicable; NR - not reported; s.c. - subcutaneous

Gross et al. (1974) reported the result of a series of feeding experiments using rats fed chrysotile and crocidolite in butter in concentrations of 5-10 mg/day for 21 months. The data were the unpublished results of various experiments conducted over the previous 10 years by three different laboratories. No evidence of cancer or any other type of lesion was found from feeding "high" asbestos by gavage in butter or margarine for $\leq$21 months. No evidence of asbestos penetration in the GI mucosa was found. The experiments were flawed because of small numbers in each group, limited administered doses and, most importantly, systematic histological examination was done on only 53 of over 200 animals. Further information on experimental procedures was not provided.

In groups of 25 male and female 10-week old Wistar rats fed 20 mg chrysotile asbestos/day (50 mg/kg bw/day) throughout their lifetime, 12/42 malignant tumors developed in the animals (4 kidney carcinomas, 1 lung carcinoma, 3 reticular cell sarcomas, 4 liver-cell carcinomas) which had an average survival time of 441 days (Gibel et al., 1976). One lung adenoma, 2 cholangiomas, 2 papillomas of the forestomach and 2 mammary fibroademonas were also observed. This result was statistically significant ($p<0.01$) compared with two malignant tumors in the control group. In the asbestos-exposed animals, four of the malignancies were kidney carcinomas, four were liver carcinomas, three were lymphomas and one was a lung carcinoma. While the filtering material was stated to contain 52.6% chrysotile asbestos, sulphated cellulose and a condensation resin, the absence of specific details on the other materials present is a serious deficiency. Among 50 animals fed 20 mg/day talc (50 mg/kg/day) for life with an average survival time of 649 days, 3/45 developed liver carcinomas and 4/45 mammary fibroadenomas were seen, a result that did not differ from the control group, which had 2/49 liver carcinomas and 5/49 mammary fibroadenomas and an average survival time of 202 days.

Cunningham et al. (1977) conducted two lifetime feeding studies on a limited number of male Wistar rats. One percent Johns Manville No. 7RF02 chrysotile asbestos (#fNR, DNR) with 5% corn oil was added to a rat chow diet and fed to groups of 10 and 40 rats in two separate experiments. In the first study, 6/7 surviving animals were found with tumors, whereas one malignancy was observed in eight controls. No GI cancers were observed but two malignancies in the asbestos-fed animals were kidney nephroblastomas. In the second study, malignancies were observed in 11/40 asbestos-fed animals and 11/40 control animals. Two of the malignancies in the asbestos-fed group were in the GI tract; one of the malignancies in the control group was a nephroblastoma, which lessens the significance of these tumors in the asbestos group. The authors concluded that small amounts of asbestos can penetrate the lining of the GI tract but no conclusions could be drawn as to the carcinogenic potential of ingested asbestos.

Smith et al. (1980) studied six groups of 60 two-month-old hamsters exposed to 0.5, 5 or 50 mg/ℓ (#fNR) of UICC amosite (DNR) and Reserve Mining Co. taconite tailings (DNR) in drinking water. Filtered water from Lake Superior was given to 120 control animals. In the low and intermediate amosite exposure groups, 4 malignancies [1 lung carcinoma, 2 stomach squamous cell carcinomas (noninvasive), 1 peritoneal mesothelioma] were found. However, no malignancies were identified in the highest exposure group and the authors did not attribute the observed malignancies to the asbestos exposure because of the absence of a consistent dose-response gradient.

Donham et al. (1980) initiated a lifetime study of male and female F344 rats fed 10% (#fNR) milled UICC Canadian chrysotile B (DNR) in their diet. Similar numbers of colon cancers were observed in the exposed group (4/189), a group fed 10% cellulose fibers (2/197) and an undosed control group (3/115). The differences in the number of colon tumors were not significant. Actuarial analysis indicated that the asbestos-fed rats were at a greater risk for developing lesions (17.9%) than the cellulose-fed rats (13.6%) and control animals (8.2%). These differences are not statistically significant when comparing the asbestos-fed group with the other two groups. Although the development of colon tumors was not statistically different at the $p<0.05$ level, the authors concluded that the ingested asbestos may have had some role in colon carcinogenesis as evidenced by electron micrographs showing penetration by asbestos fibers in the lining of the GI tract, lowered cAMP levels and an increased cumulative risk in asbestos-fed animals to develop colon lesions.

Ward et al. (1980) also investigated the cancer-promoting potential of ingested asbestos. UICC amosite (DNR) was administered to 21 rats intragasticly 3 times per week for 10 weeks at a dose of 10 mg (#fNR). No malignant tumors were reported after 34 weeks of observation. When UICC amosite was again administered with saline at the same dose for the same time period but the 50 animals were observed for 95 weeks, 17 tumors (16 carcinomas of the colon, 1 carcinoma of the ileum) were reported in 49 animals examined. No concurrent controls were observed but the incidence greatly exceeded that of 1% reported in historical controls (0/21 tumors by saline and 0/21 untreated). Groups of rats were also exposed to azoxymethane subcutaneously plus UICC amosite (DNR) or chrysotile B (DNR) by intragastric administration. Single agent and untreated controls were also studied. This study is limited by the short administration period of the asbestos. If the asbestos acts as a promoter, it would have been desirable to have continued administration to assure the presence of fibers at potential sites of cancer over the lifetime of the animals. Notably, however, the amosite with 30 week study duration clearly showed a significant increase whereas shorter duration study groups i.e., 34 weeks for amosite and chrysotile showed no response.

A study by Hilding et al. (1981) was designed to investigate the potential carcinogenic effect of taconite tailings, Johns Manville Paper-bestos No. 5 chrysotile and UICC amosite, UICC amosite only, and diatomaceous earth in drinking water and in cottage cheese. Groups of 22-30 rats were supplied water with these various materials throughout their lifetime. A variety of malignancies were found in each exposure group, although none were attributable to asbestos exposure. However, a pleural mesothelioma was identified in a group exposed to amosite plus chrysotile and a peritoneal mesothelioma was identified in the diatomaceous earth exposed group. A study by Bolton et al. (1982) examined the carcinogenic effects of asbestos on groups of 22-24 rats fed 250 mg/week (#fNR) of UICC amosite (DNR), UICC crocidolite (DNR) or UICC chrysotile (DNR) in margarine for ≤25 months. No excess malignancies were found in the exposed group compared with the margarine or undosed control groups.

Four studies on the chronic effects of dietary exposure to fibers have been published by the NTP (1982a,b,c, 1985) and presented by McConnell et al. (1983a,b). Two of these studies investigated the effects of dietary exposure to amosite and chrysotile asbestos in Syrian golden hamsters (NTP, 1982a,b; McConnell, 1983a). Groups of ~240 male and female hamsters were fed 1% asbestos by weight (#fNR) in pellets of either amosite (median length 4.37 µm; median diameter 0.72 µm; 3466×10^6 f/g) or 1 of 2 samples of chrysotile asbestos [one short range (SR) (median length 0.66 µm; median diameter 0.059 µm; 6081×10^8 f/g) and the other intermediate range (IR) in length (median length 0.82 µm; median diameter 0.0089 µm; 1291×10^8 f/g)] in test diets. Male and female groups of ~175 animals were fed IR chrysotile and oral doses of 4 mg/kg 1,2-dimethylhydrazine dihydrochloride (DMH) every other week for 10 weeks. For each exposure group four male and four female control groups of ~125 animals each were studied. Male and female control groups of ~125 animals each were exposed to DMH alone. The only group to show a significant ($p<0.05$) increase in overall primary tumors was the chrysotile group. This increase was due primarily to adrenal cortex tumors. Male hamsters receiving SR chrysotile or the combined DMH/IR chrysotile exposure also showed an overall primary tumor increase relative to pooled controls. However, when survival differences were taken into account, the excesses were not statistically significant. Significant increases in cortical adenomas were seen in male and female IR chrysotile-exposed groups when compared with pooled controls, but not when compared with temporal controls. None of the treated groups showed an increased risk of malignancy in the GI tract. The absence of GI tumors was believed to weaken any association of adrenal tumors with chrysotile exposure. None of the male or female animals that were administered DMH, with or without chrysotile asbestos, showed significant increases in intestinal cancer. Thus, under the conditions of the bioassay, amosite asbestos SR or IR chrysotile asbestos were not shown to be carcinogenic when ingested by male and female Syrian golden hamsters. The carcinogenic studies of the combined exposure to IR chrysotile asbestos and DMH are considered inadequate because of no increase in intestinal neoplasia in the DMH group.

Experiments similar to the hamster studies have been conducted by McConnell et al. (1983b) and NTP (1982c) to determine the chronic effects of ingestion of Penge, Transvaal, Republic of South Africa amosite asbestos and Governeur, NY nonfibrous tremolite in F344 rats. One percent tremolite or amosite asbestos (median length 4.37 μm; median diameter 0.72 μm; 3466x10^6 f/g) by weight (#fNR) was incorporated into the animals diet and fed to groups (n=100-250) of male and female rats for their lifetime (this includes prenatal exposure as a result of dams being fed asbestos during gestation). Male and female animals, in groups of 175 each, were exposed to amosite and 5-15 mg/kg DMH. Positive controls of 125 male and 125 female animals were exposed to DMH alone. Male and female groups of 100 rats were given 470 mg/kg bw chrysotile by gavage before weaning (21 days postpartum) and subsequently fed the amosite diet. A significantly increased incidence of C-cell carcinoma of the thyroid was found in amosite-treated male rats. Nonsignificant increases were seen in female rats and both the male and female groups that underwent preweaning gavage. No excess neoplasms of the GI tract were found in any treated group, nor were any excess carcinomas found at any site in the tremolite-exposed rats. A very high incidence of GI neoplasia was experienced by the DMH and the DMH-amosite groups. However, the overall incidences of cancer at different sites were similar in the DMH and DMH-amosite groups, but some specific differences occurred. For example, 11% of the DMH-amosite group developed cancer of the duodenum versus 2% of the controls. On the other hand, 9% of the DMH controls developed neoplasms of the jejunum versus 1% in the DMH-amosite group.

Overall, the data suggest that amosite asbestos has neither a cocarcinogenic nor protective effect on the carcinogenic potential of DMH. However, the very high incidence of cancer in the DMH-exposed groups precluded a definitive statement on the role of asbestos as a cocarcinogen or promoter. Under the conditions of the lifetime bioassay, neither tremolite nor amosite asbestos was found to be carcinogenic when ingested at the level of 1% diet in male and female F344 rats.

In a more recent study, groups of 88-250 male and female F344 rats were exposed to 1% chrysotile asbestos fibers [Union Carbide Corp., COF-25 SR (median length 0.66 μm; median diameter 0.059; 6081×10^{-6} f/g) and Johns Manville Co., Plastobest-20 IR (median length 0.82 μm; median diameter 0.089, 1291×10^{6} f/g)] in their diet as part of a lifetime carcinogenicity study (NTP, 1985). Exposure began with the dams of the test animals. A subgroup of 100 male and female chrysotile exposed rats received 0.47 mg/g of the IR fibers in drinking water by gavage during lactation. At 9 weeks of age, another subgroup of 125-175 control and asbestos-exposed rats were given DMH (7.5 mg/kg for males, 15 mg/kg for females) by gavage every other week for 10 weeks (5 doses). No signs of maternal or fetal toxicity were observed in the asbestos exposure group. Males and females exposed over their lifetime also showed no overt signs of toxicity. Benign epithelial neoplasms (adenomatous polyps), however, were found in the large intestine of some male rats (9/250, p=0.08) fed the IR asbestos. The incidence of these neoplasms was highly significant (p=0.003) when compared with the incidence of epithelial neoplasms (benign and malignant) in male controls (3/524). Therefore, NTP (1985) claimed there was "some" evidence of carcinogenicity in male rats exposed to IR chrysotile fibers. No evidence for carcinogenicity was found in male and female rats exposed to the SR fibers. The coadministration of DMH and IR asbestos "did not indicate that IR chrysotile asbestos had either a tumor-enhancing or protective effect" (see Chapter VIII).

In summary, three animal studies (Gibel et al., 1976; Ward et al., 1980; NTP, 1985) demonstrated that asbestos fibers can be associated with GI tumorigenicity (benign and malignant). Chrysotile and amosite seem to produce a response in rats although the responsibility is not clear. Taken as a whole, the oral studies data base covering different types of fibers, rats and hamsters, about 15 different authors with many more specific individual bioassays do not present a consistent picture of carcinogenicity. Many studies, however, involved very few animals and an occasional suggestive tumor, such as mesothelioma, that could not be unequivocably associated with the asbestos exposure. Conversely, positive studies, such as that of Gibel et al. (1976), were marred because of the absence of information on possible exposures to other carcinogenic materials. The NTP (1982a,b,c) studies on the ingestion of amosite and chrysotile asbestos by hamsters and amosite asbestos by F344 rats at the 1% level did not indicate any carcinogenic effect of ingested asbestos. In the NTP (1985) male rats ingesting IR chrysotile fibers at 1% in the diet had a significant increase in benign epithelial neoplasms in the large intestine. The overall animal evidence is adequate to reinforce the concern for the carcinogenic potential of asbestos by ingestion exposure, as would be inferred from the quite strong human data base on inhalation exposure. The additional strong association of GI cancers with inhalation exposure and the various hypotheses of how the ingestion exposure occurs further add to the qualitative evidence that under certain conditions ingestion may pose some human risk, albeit fiber characteristics and exposure regime may play a role. The strength or weakness of the dose-reponse information for ingestion exposure via the drinking water vehicle is a separate question. This is interpreted as limited evidence that ingested chrysotile asbestos fibers may be carcinogenic. Further research is needed to clarify this issue.

Intraperitoneal Administration -- Intraperitoneal injections of 20 mg (#fNR) crocidolite (DNR) or chrysotile (DNR) produced three peritoneal mesotheliomas in 13 CD rats. No tumors were produced by 20 mg (#fNR) of amosite (DNR) in a group of 11 rats (Maltoni and Annoscia, 1974). The same investigators also injected 25 mg (#fNR) crocidolite into 50 male and 50 female 17-week-old Sprague-Dawley rats and observed 31 mesothelial tumors in males and 34 in females.

In an extensive series of experiments, Pott and Friedrichs (1972) and Pott et al. (1976) produced peritoneal mesotheliomas in mice and rats injected with various commercial varieties of asbestos and other fibrous material. These results are shown in Table V-3. With use of ball-milled in comparison to native fibers, the rate of tumor production was reduced from 55% to 32% and the time from onset of exposure to first tumor was lengthened from 323 days to 400 days following administration of four doses of 25 mg (#fNR) UICC Rhodesian chrysotile A (DNR). In the case of the ball-milled fiber, 99% were reported to be <3 μm in length, 93% <1 μm and 60% <0.3 μm. The data suggest that large-diameter fibers (>3 μm) are more carcinogenic than finer fibers. The reduced carcinogenicity of shorter, ball-milled fibers may also be a by-product of the abrasive procedure used

TABLE V-3

Tumors in Abdomen and/or Thorax after Intraperitoneal Injection of Glass Fibers, Crocidolite or Corundum in Rats[a]

Dust[b]	Form[c]	Dose (mg)	Effective No. of Dissected Rats	No. of Days Before First Tumor	Average Survival Time of Rats with Tumors (days after injection)	Rats with Tumors (%)	Tumor Type[d]					
							1	2	3	4	5	6
Glass fibers MN 104	f	2	73	421	703	27.4	17	3	-	-	1	1
Glass fibers MN 104	f	10	77	210	632	53.2	36	4	-	1	3	-
Glass fibers MN 104	f	2x25	77	194	367	71.4	47	6	2	-	-	-
Crocidolite, UICC (DNR)	f	2 (ØFNR)	39	452	761	38.5	12	3	-	-	2	1
Corundum	g	2x25	37	545	799	8.1	1	-	-	2	2	2
UICC Rhodesian chrysotile A (DNR)	f	2 (ØFNR)	37	431	651	16.2	4	2	-	-	1	-
UICC Rhodesian chrysotile A (DNR)	f	6.25 (ØFNR)	35	343	501	77.1	24	3	-	-	-	-
UICC Rhodesian chrysotile A (DNR)	f	25 (ØFNR)	31	276	419	80.6	21	2	1	1	-	-
UICC Rhodesian chrysotile A (DNR)	f	4x25 (ØFNR)	33	323	361	54.5	16	2	-	-	-	-
UICC Rhodesian chrysotile A (DNR)	f	3x25 (ØFNR) s.c.	33	449	449	3.0	-	-	1	-	-	-
UICC Rhodesian A (DNR)	f	4x25 (ØFNR)	37	400	509	32.4	9	3	-	-	-	-
Palygorscite	f	3x25	34	257	348	76.5	24	2	-	-	-	-
Glass fibers S + S 106	f	2	34	692	692	2.9	1		-	-	-	-
Glass fibers S + S 106	f	10	36	350	530	11.1	2	2	-	-	1	-
Glass fibers S + S 106	f	4x25	32	197	325	71.9	20	3	-	-	-	-

TABLE V-3 (cont.)

Dust[b]	Form[c]	Dose (i.p.) (mg)	Effective No. of Dissected Rats	No. of Days Before First Tumor	Average Survival Time of Rats with Tumors (days after injection)	Rats with Tumors (%)	Tumor Type[d]					
							1	2	3	4	5	6
Gypsum	f	4x25	35	579	583	5.7	-	-	1	1	1	-
Nemalite	f	4x25	34	249	315	73.5	17	8	-	-	-	-
Actinolite	g	4x25	39	-	-	-	-	-	-	-	-	-
Biotite	g	4x25	37	-	-	-	-		-	-	-	-
Haematite (precipit.)	g	4x25	34	-	-	-		-	-	-	-	-
Haematite (mineral)	g	4x25	38	-	-	-	-	-	-	-	-	-
Pectolite	g	4x25	40	569	569	2.5	-	-	-	1	1	1
Sanidine	g	4x25	39	579	579	2.6	-	1	-	-	-	-
Talc	g	4x25	36	587	587	2.8	1	-	-	-	-	-

TABLE V-3 (cont.)

Dust[b]	Form[c]	Dose (i.p.) (mg)	Effective No. of Dissected Rats	No. of Days Before First Tumor	Average Survival Time of Rats with Tumors (days after injection)	Rats with Tumors (%)	Tumor Type[d]					
							1	2	3	4	5	6
NaCl (control)	-	4x2ml	72	-	-	-	-		-	-	-	-

[a]Source: Adapted from Pott and Friedrichs, 1972; Pott et al., 1976

[b]Type of asbestos and dimensions (dimensions dependent on method of preparation):

	Modal Length (μm)	Modal Width (μm)
Crocidolite, UICC (South African)	0.6	0.13
Amosite, UICC (South African)	1.4	0.14
Tremolite (Montana) UICC	5.1	0.17
Anthrophyllite, UICC (Finnish) from Langer et al., 1974 (ultrasonically dispersed in water)	5.1	0.18
Chrysotile, NIEHS Short Range (SR), (Calif., Union Carbide)	0.66	0.059
Chrysotile NIEHS Intermediate Range (IR), (Quebec, Johns Manville-Plastobest-20) from NTP, 1985	0.82	0.089
	Range of Mean (μm)	Range of Mean (μm)
Chrysotile (Quebec) from Atkinson et al., 1971 (after milling)	1000-2000	0.030-0.038

[c]f = fibrous; g = granular

[d]Tumor types are: 1 = mesothelioma; 2 = spindle cell sarcoma; 3 = polymorphous sarcoma; 4 = carcinoma; 5 = reticulum cell sarcoma; 6 = benign - not evaluated in tumor rates

to create these fibers. Langer et al. (1978) demonstrated a dose-response relationship between length of milling time and the reduction in crystallinity of the fiber. This was accompanied by changes in surface chemistry and decreased biological activity. Animal studies using short fibers created by less vigorous methods have shown greater biological response than studies using fibers created by ball milling. Furthermore, the extrapolation of data developed on size-dependent effects, from intrapleural or i.p. administration to inhalation (where movement of the fibers in airways and subsequently through body tissues is strongly size-dependent) presents significant difficulties. Finally, since the number of smaller fibers in an exposure circumstance may be 100 times greater than those >5 μm in length, the reduction of their carcinogenicity must be demonstrated at a level 100 times less before their contribution can be neglected.

Intrapleural Administration -- Intrapleural injections of 25 mg (#FNR) chrysotile (DNR) or amosite (DNR) into hamsters produced tumors diagnosed as pleural mesotheliomas (Smith et al., 1965). When three groups of 50 hamster were treated with the same dose level, 8-10 such tumors were reported in each group (Smith et al., 1972).

Smith (1973) also gave right pleural injections of 25 mg (#FNR) of commercial talcs (Whittahen, Clark and Daniels, Inc.) containing tremolite asbestos (DNR) suspended in 0.5 mℓ saline to 50 hamsters. Animals were followed for their lifetime and no tumors attributable to the treatment were found.

Mutagenicity. In a preliminary study, chromosomal aberrations were seen in Chinese hamster cells cultured in a medium containing 0.01 mg/mℓ (#fNR) of either SFA chrysotile (DNR) or UICC crocidolite (Sincock and Seabright, 1975). No chromosomal aberrations were seen in culture with coarse glass fibers or with control media. A more extensive series of experiments by Sincock (1977), using several chrysotile (DNR) and crocidolite (DNR) samples, showed that both positive transformation of morphology and positive genetic responses result from the passive inclusion of asbestos in culture media of CHO-K1 Chinese hamster cells. Very fine fibrous glass produced the same abnormalities seen in untreated cultured cells. The principal results are shown in Table V-4.

Chamberlain and Tarmy (1977) tested UICC Canadian chrysotile, UICC amosite, UICC anthophyllite and superfine Canadian SFA chrysotile on several strains of Escherichia coli and Salmonella typhimurium bacterial systems in which mutagenicity to exogenous materials appears to correlate well with animal carcinogenic test data. E. coli tester strains included the following: B/r, WP2, WP2 uvrA and WP2 uvrA polA. Testing of asbestos for mutagenicity in S. typhimurium was limited to investigation of tester strains TA1535 and TA1538. No more recent studies were available providing data on testing of asbestos in the more sensitive strains TA98 and TA100. Doses ranged from 1-5000 μg/ℓ of asbestos for 72 hours. Several positive and negative controls were used in all experiments. No mutagenic activity was associated with asbestos over the wide range of concentrations for either test system. The authors pointed out that prokaryotic cells (bacteria) do not phagocytize the fibers as do eukaryotic cells, such as macrophages.

TABLE V 4

Effects of Different Treatments on Chromosomes of CHO-K1 Chinese Hamster Cells*

Effect	SFA Chrysotile	Rhodesian Chrysotile a	Canadian Chrysotile b	UICC Crocidolite	UICC Anthophyllite	UICC Amosite	Glass 110	Control
Polyploids	28	23	27	26	2	14	3	4
Cells with fragments	13	14	11	10	10	16	0	0
Other abnormalities	33	9	15	29	9	13	0	0
Percent abnormal karyotypes	62	34	39	56	26	41	3	4

Effect	Rhodesian Chrysotile a	Rhodesian Chrysotile a Leached	Canadian Chrysotile b	Canadian Chrysotile b Leached	UICC Crocidolite	UICC Crocidolite Milled	Glass 110	Control
Polyploids	23	6	26	10	26	6	6	4
Cells with fragments	13	0	9	0	14	9	0	0
Other abnormalities	10	0	16	4	28	3	0	0
Percent abnormal cells	34	6	42	14	57	16	6	4

*This table summarizes the principal results reported in Sincock, 1977. Results were obtained using 48-hour exposure; 100 cells were scored from each culture. Categories of genetic damage were not mutually exclusive.

Chrysotile, crocidolite and amosite asbestos appeared to have no independent mutagenic capability in testing of Syrian hamster embryo cells (Newman et al., 1980), but after 20 hours of interaction between chrysotile asbestos and the cultured cells, alterations were observed in glycolipids and glycoproteins located in the cell membrane surface. Since these changes were observed after prolonged exposure of the cells to asbestos, the data support the concept that a metabolic rather than a masking effect is involved. The authors theorize that the membrane changes incurred by asbestos serve to allow other mutagens to pass into the cell so as to act on the nuclear structure; however, this theory has not been experimentally pursued.

Teratogenicity/Reproductive Effects. Schneider and Maurer (1977) gave pregnant CD-1 mice (10-12/dose) 4, 40 or 400 mg Johns Manville No. 7RF02 chrysotile asbestos/kg bw (1.43, 14.3 or 143 mg asbestos/mℓ) in their drinking water during days 1-15 of gestation. Water consumption did not vary between the different dosage groups. There was also no difference in embryo survival between the treatment groups and the controls, which received only tap water. There were no signs of maternal toxicity.

In a second study, Schneider and Maurer (1977) cultured 4-day-old mouse blastocysts in 1, 10 or 100 μg Johns Manville No. 7RF02 chrysotile asbestos for 4 hours. The blastocysts were then transferred to day 3 or day 4 pseudo-pregnant mice. There were no significant differences in the rate of implantation between the Johns Manville No. 7RF021 chrysotile asbestos exposed blastocysts and the controls. There was, however, a difference in fetal viability. A significant dose dependent relationship was reported in the number of dead and resorbed fetuses in the day 3 ($p=0.05$) and day 4 ($p=0.06$) pseudo-pregnant mice. It should be noted that the authors' level of significance was established as $p<0.10$. No dose-response relationships were observed in the postimplantation mortality in day 4 mice. The day 3 mice were stated to show a dose-dependent increase in fetal mortality ($p<0.05$). Other signs of fetotoxicity (decreased fetal weight, stunted fetuses and malformations) were not significantly different between the controls and asbestos exposure groups. Electron micrographs indicated that the zona pellucida protected the trophoblast cells of the blastocyst from asbestos fibers.

The evidence supplied by Cunningham and Pontefract (1974) of transplacental transfer of Johns Manville Co. No. 7RF02 chrysotile (length 0.5-2.0 µm; diameter NR) asbestos (9.4×10^{8} f/mℓ) supports the possibility of the occurrence of teratogenic or reproductive effects following asbestos exposure (see Chapter III the Absorption and Distribution:Injection of Asbestos Section).

Summary

General toxicity following the ingestion of asbestos is minimal with no specific target organ defined. Asbestos is considered to be a human carcinogen, U.S. EPA weight-of-evidence category A. The qualitative evidence for human carcinogenicity and the dose-response data base for risk analysis is quite strong for the inhalation exposure route. For exposure by ingestion, the qualitative data base is also strong based on observations from inhalation epidemiology studies and some suggested observations from ingestion epidemiology studies. Some positive responses in the rat confirm that asbestos has the potential for human carcinogenicity by the oral route. However, the suitability and reliability of the data to estimate the carcinogenic risk from exposure to asbestos by ingestion is much weaker than the data base for exposure by inhalation. In addition, many of the studies suffered from serious limitations. From the studies reviewed, limited in both number and scope, asbestos has not been demonstrated to be either mutagenic or teratogenic. Data on the health effects of asbestos in animals are provided and summarized in Tables V-I and V-2.

VI. HEALTH EFFECTS IN HUMANS

Human health effects associated with the ingestion of asbestos have centered around carcinogenicity. No known chronic nonmalignant effects have been associated with the ingestion of asbestos or other fibers in water. Effects in humans associated with acute exposures have been restricted to the identification of asbestos fibers in the urines of individuals ingesting the substances in water or other materials (Cook and Olson, 1979). The finding of fibers in body fluids has not been associated with any health effects. Auerbach et al. (1977) reported that the ingestion of Duluth water contaminated with amosite (DNR; 14-600x10^{6} f/ℓ) did not result in a great increase in the number of asbestos bodies present in lung tissue as viewed under a light microscope. Carter and Taylor (1980) examined liver, jejunum and lung tissue samples of persons with long-term ($\leq$15 years) high-level oral exposure to amosite asbestos (average fiber size = 1.5x0.2 μm; 2x10^{7} f/ℓ) in Duluth, MN. This fiber type was found in significant numbers (60%) in the study group. The differences in concentration between tissues studied was not statistically significant. Greatest amounts were found in the lung followed by the liver and jejunum.

An understanding of the effects of inhaled asbestos fibers is important in discussing the effects of ingesting asbestos fiber. This former exposure results not only in lung cancers but in cancers at extrathoracic sites as well. Inhaled asbestos fibers are thought to penetrate the lung parenchyma and circulate in the lymph to other organs in the body. The consistency of an increased cancer risk from inhaled fibers at extrathoracic sites, and its magnitude, either in absolute (observed-expected deaths) or relative (observed/expected deaths) terms, is less for cancer at other sites than for lung cancer. Nevertheless, many occupational studies document significant cancer risks at various GI sites. Cancer of the kidney has also been found to be significantly elevated in two large studies (Selikoff et al., 1979; Puntoni et al., 1979). Among female workers exposed to crocidolite, chrysotile or amosite asbestos or a combination, ovarian cancer has been found in excess (Newhouse et al., 1972). While no other specific sites have been shown to be elevated at the 0.05 level of significance, the category of all cancers other than lung, GI tract or mesothelial is significantly elevated (Selikoff et al., 1979).

Table VI-1 lists all studies in which >10 GI cancers were expected or observed and in which the overall lung cancer risk was elevated at the 0.05 level of significance. This choice eliminated many small studies from consideration, which have statistically uncertain data, as well as several large studies that demonstrated a low risk of lung cancer, either because of exposure or follow-up circumstances. Because the excess risk of GI cancer is less than that of the lung, significantly elevated risks are unlikely to be seen in studies that demonstrate little lung cancer risk. Negative data in such studies do not carry great significance. Data in Table VI-1 show that all but one of the listed studies has an excess GI cancer risk, albeit in three studies the risk is small. However, 10 of the 23 studies demonstrate the risk at a 0.05 level of significance. Figure VI-1 displays the relationship between the relative risk of lung cancer and relative risk of GI cancer in the 12 studies with excess GI cancer risk. A consistent relationship exists between a greater GI cancer risk and an increased lung cancer risk. The GI tract obviously is exposed to fibers because the majority of inhaled fibers are brought up from the respiratory tract and

TABLE VI-1

Observed and Expected Deaths for Various Causes in Selected Mortality Studies[a]

Type of Asbestos and Fiber Dimensions	Respiratory Cancer ICD 162-164			Digestive Cancer ICD 150-159				Other Cancers ICD except 150-159, 162-164, meso				Reference
	O	E	O-E	O	E	O-E	$\frac{(O-E)_d}{(O-E)_r}$	O	E	O-E	$\frac{(O-E)_o}{(O-E)_r}$	
Chrysotile, Crocidolite and Amosite (DNR)	63	23.3	39.7	55	39.9	15.1	0.380	55	45.6	9.4	0.237	Henderson and Enterline, 1979
Chrysotile (DNR)	230	184.0	46.0	276	272.4	3.6	0.078	237	217.4	19.6	0.426	McDonald et al., 1980
Crocidolite, Chrysotile, Amosite (DNR)	103	43.2	59.8	40	34.0	6.0	0.100	38	27.4	10.6	0.177	Newhouse and Berry, 1979 (male)
Crocidolite Chrysotile and Amosite (DNR)	27	3.2	23.8	20	10.2	9.8	0.412	33	20.4	12.6	0.529	Newhouse and Berry, 1979 (female)
Chrysotile and Amosite (DNR)	93	13.3	79.7	43	14.8	28.2	0.353	28	24.5	3.5	0.044	Selikoff et al., 1979 (NY-NJ)
Chrysotile and Amosite (DNR)	390	93.7	296.3	89	53.2	35.8	0.121	184	131.8	52.2	0.176	Selikoff et al., 1979 (U.S.)
Chrysotile (DNR)	25	11.1	13.9	10	9.5	0.5	0.036	14	16.1	(-2.1)	def.	Nicholson et al., 1979
Type not reported	51	23.8	17.2	16	15.7	0.3	0.019	18	24.8	(-6.8)	def.	Peto, 1977
Type not reported	30	9.8	20.2	15	7.1	7.9	0.527	20	6.8	13.2	0.653	Mancuso and El-attar, 1967
Type not reported	123	54.9	68.1	94	76.6	17.4	0.255	88	81.3	6.7	0.098	Puntoni et al., 1979
Amosite (DNR)	83	21.9	61.1	28	22.7	5.3	0.087	39	35.9	3.1	0.037	Seidman et al., 1979
Canadian and Rhodesian Chrysotile (DNR) 2.7-6.9 f>5 µm/cc	33	9.8	23.2	10	8.1	1.9	0.082	11	14.1	(-3.1)	def.	Dement et al., 1983a,b
Crocidolite and Chrysotile (DNR)	12	6.3	5.7	10	20.3	(-10.3)	def.	35	39.5	(-4.5)	def.	Jones et al., 1980

TABLE VI-1 (cont.)

Type of Asbestos and Fiber Dimensions	Respiratory Cancer ICD 162-164			Digestive Cancer ICD 150-159				Other Cancers ICD except 150-159, 162-164, meso				Reference
	O	E	O-E	O	E	O-E	$\frac{(O-E)_d}{(O-E)_r}$	O	E	O-E	$\frac{(O-E)_o}{(O-E)_r}$	
Canadian and Rhodesian Chrysotile (DNR), some Crocidolite (DNR)	59	29.6	29.4	26	17.1	8.9	0.302	35	27.7	7.4	0.252	McDonald et al., 1983
Canadian Chrysotile (DNR), some Anthophyllite and Crocidolite	73	49.1	23.9	59	51.6	7.4	0.309	70	60.4	9.6	0.402	McDonald et al., 1984
Chrysotile (~99%, DNR), Amosite (~1%, DNR), Crocidolite (<1%, DNR)	49	36.1	12.9	50	41.4	8.6	0.667	69	51.2	17.8	0.380	Robinson et al., 1979
Penge, Transvaal, So. Africa Amosite (≥97%, DNR) Chrysotile (<3%, DNR)	57	29.1	27.9	19	17.1	1.9	0.068	33	28.2	4.8	0.172	Acheson et al., 1984
Western Australian Crocidolite (DNR)	10	3.7	6.3	7	10.7	(3.7)	def.	35	21.6	13.4	2.127	Wignall and Fox, 1982
Finnish Anthophyllite	21	12.6	8.4	7	14.9	(7.9)	def.	no data				Meurman et al., 1974
Chrysotile (90%, DNR), some Amosite (DNR) and Crocidolite (<1%, DNR)	12	6.6	5.4	19	10.8	8.2	1.519	21	20.4	0.6	0.111	Albin et al., 1984

TABLE VI-1 (cont.)

Type of Asbestos and Fiber Dimensions	Respiratory Cancer ICD 162-164			Digestive Cancer ICD 150-159				Other Cancers ICD except 150-159, 162-164, meso				Reference
	O	E	O-E	O	E	O-E	$\frac{(O-E)_d}{(O-E)_r}$	O	E	O-E	$\frac{(O-E)_o}{(O-E)_r}$	
Type not reported	24	5	19	13	1	12	0.632	10	no data			Elmes and Simpson, 1977
Chrysotile (length: 0.4-29% f >5μ, diameter NR)	27[c]	8.4	18.6	13[c]	5.0	8.0	0.430	17[c]	14.4	2.6	0.140	Nicholson, 1976
Type not reported	44	27.3	16.7	31	29.9	1.1	0.066	89	93.9	(4.9)	def.	Clemmesen and Hjalgrim-Jensen, 1981

[a] Source: Adapted from U.S. EPA, 1986a

[b] Excess risk may not be asbestos-related

[c] Best estimate data on causes of death

O = observed deaths; E = expected deaths; d = digestive cancer; r = respiratory cancer; o = other cancer; def. = no ratio when deficient in O-E (i.e., O<E); DNR = dimensions not reported, ICD= International Classification of Diseases

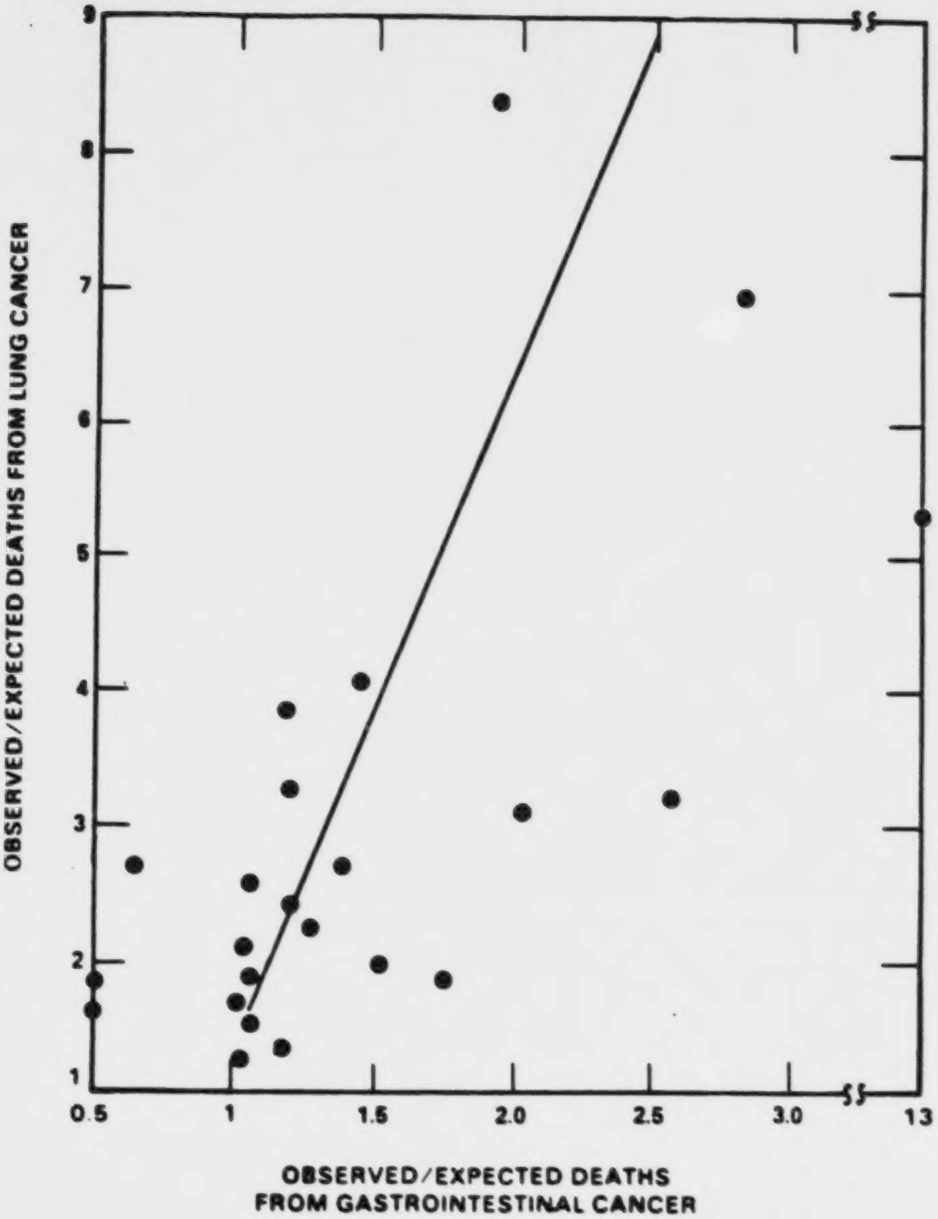

FIGURE VI-1

The ratio of observed to expected mortality from lung cancer versus the ratio of observed to expected mortality from gastrointestinal cancer.

Source: U.S. EPA, 1986a

swallowed (Morgan et al., 1975). Additionally, some fibers may become entrapped within the gut wall (Storeygard and Brown, 1977). Never- theless, the magnitude of the excess fibers at GI sites is much less than that for the lung. In recent studies, the GI excess is ~10-30% of the lung excess.

The number of studies demonstrating a statistically significant excess risk of GI cancer in asbestos-exposed groups and the correlation of the relative risk of GI with the relative risk of lung cancer are highly suggestive of a causal relationship between asbestos exposure and GI cancer. However, alternative interpretations of the above data are possible. Doll and Peto (1985) have suggested that many of the excess cancers attributed to GI sites may be misdiagnosed lung cancers or mesotheliomas. They also cite the absence of confirmatory animal data showing a risk of cancer at extrapulmonary sites as weighing against a causal relationship. However, it is difficult to accept that all excess GI cancers are the result of misdiagnosis. While cancers of some of the GI sites, particularly the pancreas and the stomach to some extent, are often misdiagnosed mesotheliomas, cancer of the colon and rectum are usually correctly certified and the excesses at these sites across studies are unlikely to be the result of misdiagnosis.

The U.S. EPAs Carcinogen Assessment Group has reviewed studies with excess GI cancers and have concluded that the association between GI cancer excess and asbestos exposure is strong.

Table VI-1 also lists the observed and expected mortality for cancers other than mesothelioma and the GI or respiratory tract. The elevation is not as consistent as that for GI cancer. Only three studies have elevated risks that are significant at the 0.05 level, and deficits are observed in four. The analysis is further complicated by the possibility that misclassification of lung cancer or mesothelioma may have occurred for some cases. For example, brain or liver cancers could be metastatic lung cancers in which the primary cancer was not properly identified. In the study of insulators, Selikoff et al. (1979) found that 26/49 pancreatic cancers were misclassified; most of the misclassified were peritoneal mesotheliomas. As with GI cancer, the excess at other sites is much less than the excess for lung cancer and generally less than that for GI cancer.

Unlike the situation of the inhalation of asbestos fibers, no mesothelioma case reports or case control studies document the role of ingested asbestos in drinking water in the etiology of the disease. This may be the result of an overall lower risk of disease from sources of ingested asbestos compared with those from inhaling air around factories or in the homes of workers. Potential cases of mesothelioma caused by ingestion would easily be lost in a background of cases with no attribution. In humans, the only possibility of identifying a carcinogenic effect from ingestion with water is to do large scale epidemiologic studies. Several studies have been published that investigate the possibility of carcinogenic health effects caused by ingested asbestos in six areas of the United States and one in Canada. These areas are Duluth, MN; Connecticut; San Francisco Bay; Utah; Puget Sound; Escambia County, FL and Quebec, Canada.

Epidemiological Studies

The initial concern over the presence of asbestos fibers in drinking water supplies began in 1973 after millions of mineral fibers/ℓ were reported in Lake Superior, the source of municipal water for Duluth, MN and five small communities on the lake shore. It was discovered that the source was the deposition of mine tailings (amosite) into the lake since 1955. Connecticut offered the possibility of using data collected on asbestos-cement (AC) pipe (chrysotile) and linking it with reliable cancer incidence data from the 35+-year-old tumor registry. In the San Francisco Bay area, the sources of several drinking water supplies were aquifers or reservoirs that had contact with rock containing chrysotile. In several Utah communities AC pipe (chrysotile) was used for periods exceeding 20 years. In addition, Utah is also a member of the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI) with a complete state-wide tumor registry. In the Puget Sound area of Washington State, three of the largest metropolitan areas have been serviced by water supplies containing chrysotile fibers since the early 1900s. In Escambia County, FL, asbestos fibers were detected in drinking water apparently caused by the deterioration of AC distribution mains that have been used for 30-40 years. Finally, in Quebec, Canada, environmental surveys revealed high concentrations of fibers in drinking water caused by extensive asbestos mining (chrysotile). The studies undertaken in these areas will be briefly described in this chapter. The results are summarized in Tables VI-2 and VI-3.

Two studies were initially undertaken to investigate the possible effects of amosite asbestos (DNR; $1\text{-}30 \times 10^{6}$ f/ℓ) in the municipal water of Duluth, MN. Mason et al. (1974) reviewed the age-adjusted cancer death rates for Duluth in four periods of time and compared them with those of the State of Minnesota and Hennepin County (Minneapolis). Risk ratios (Duluth/comparison group) were elevated for many GI sites, particularly males. However, higher risk ratios for many sites existed before the water supply was contaminated. The only cancer that showed a consistently increasing

TABLE VI-2

Summary of Studies of Gastrointestinal Cancer Risk in Relation to Ingested Asbestos by Cancer Site[a,b]

Gastrointestinal Cancer Site	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA		Escambia Co., FL
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
All sites combined	(++)	(--)	(00)	ns	ns	(00)	(+0)	(++)	(++)	(++)	ns	(00)	ns	ns
Esophagus	(+-)	(00)	(00)	ns	ns	(00)	(00)	(0+)	(++)	ns	ns	ns	(00)	(00)
Stomach	(++)	(+0)	(00)	(00)	(00)	(+0)	(+0)	(++)	(++)	ns	(00)	(00)	(00)	
Small intestine	ns	(00)	(00)	ns	ns	ns	ns	(00)	(00)	ns	(00)	ns	(++)	
Colon	(00)	(--)	(00)	(00)	(00)	(00)	(00)	(00)	(+0)	ns	(0-)	(--)	(00)	
Rectum	(++)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	ns	(00)	ns	(00)	
Biliary passage/liver	(00)	(00)	(00)	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	(00)	ns
Gallbladder	ns	(00)	(00)	ns	ns	ns	ns	(0+)	(00)	ns	(0+)	ns	(00)	ns
Pancreas	(0+)	(++)	(0+)	ns	(+0)	(0+)	(00)	(0+)	(++)	ns	(00)	ns	(00)	(00)
Peritoneum	ns	(00)	(00)	ns	ns	ns	ns	(++)	(0+)	ns	(00)	ns	(00)	ns

[a] Source: Adapted from Marsh, 1983

[b] (Male, female) = Association with ingested asbestos: + positive; 0 none; - negative; ns = not studied

1. Mason et al., 1974
2. Levy et al., 1976
3. Sigurdson et al., 1981
4. Harrington et al., 1978
5. Meigs et al., 1980
6. Wigle, 1977
7. Toft et al., 1981
8. Kanarek et al., 1980
9. Conforti et al., 1981
10. Tarter, 1981
11. Sadler et al., 1981
12. Severson, 1979
13. Pollissar et al., 1982
14. Millette et al., 1983

TABLE VI-3

Summary of Studies of Nongastrointestinal Cancer Risk in Relation to Ingested Asbestos by Cancer Site[a,b]

Nongastrointestinal Cancer Site	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA		Escambia Co., FL
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Buccal cavity and pharynx	ns	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	ns	ns	(00)	ns
Bronchus, trachea, lungs	(+0)	ns	(00)	ns	(00)	(+0)	(+0)	(+0)	(00)	ns	ns	ns	(00)	(00)
Pleura	ns	ns	ns	ns	ns	ns	ns	(0+)	(0+)	ns	ns	ns	ns	ns
Prostate (males only)	ns	ns	ns	ns	ns	0	0	0	+	ns	ns	ns	+	0
Kidneys	ns	ns	ns	ns	(00)	(00)	(00)	(0+)	(00)	ns	(+0)	(00)	(00)	(00)
Bladder	ns	ns	ns	ns	(00)	(00)	(00)	(00)	(00)	ns	ns	ns	(00)	(00)
Brain/CNS	(00)	ns	ns	ns	ns	(00)	(00)	(00)	(00)	ns	ns	ns	(+-)	ns
Thyroid	ns	ns	ns	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	(++)	ns
Leukemia, aleukemia	(00)	ns	ns	ns	ns	(00)	(00)	(00)	(00)	ns	(+0)	ns	(+-)	ns

[a] Source: Adapted from Marsh, 1983

[b] (Male, female) = Association with ingested asbestos: + positive; 0 none; - negative; ns = not studied

1. Mason et al., 1974
2. Levy et al., 1976
3. Sigurdson et al., 1981
4. Harrington et al., 1978
5. Meigs et al., 1980
6. Wigle, 1977
7. Toft et al., 1981
8. Kanarek et al., 1980
9. Conforti et al., 1981
10. Tarter, 1981
11. Sadler et al., 1981
12. Severson, 1979
13. Polissar et al., 1982
14. Millette et al., 1983

risk with calendar periods in both males and females was cancer of the rectum. A study by Levy et al. (1976) compared GI cancer incidence in Duluth with comparable data collected in Minneapolis and St. Paul for the years 1969-1971. Cancer of the stomach in males was significantly greater in Duluth than St. Paul, but not in Minneapolis. Colon/rectal cancer was lower in Duluth than either Minneapolis or St. Paul. The only other cancer site elevated was that of the pancreas for males and females combined.

Sigurdson et al. (1981) continued the follow-up of Duluth residents and compared Duluth rates for 1972-1974 with those of 1969-1971. Mortality rates in Duluth were substantially greater than those of Minneapolis for cancer of the stomach, small intestine and rectum in males and females, and cancer of the pancreas in females, for the years 1969-1971. However, as found in the earlier study by Levy et al. (1976), the corresponding incidence rates for both cities were quite similar. Lung cancer rates significantly increased in females and decreased in males in Duluth between 1969-1971 and 1972-1974. These changes are likely to be related to cigarette smoking habits, rather than the ingestion of the asbestos fibers. In the final study of this series (Sigurdson, 1983) Duluth rates from 1974-1976 were compared with those of 1969-1971. A decrease in cancer of the prostate and an increase in cancer of the pleura were found in males; increases in uterine cancer, multiple myeloma and cancer of the lung were found in females.

Two studies have been conducted of relatively small populations in Quebec that were exposed to exceedingly high concentrations of chrysotile (DNR; 1.1-1300x10^6 f/ℓ) in drinking water. Unfortunately, the results are in part confounded by occupational and residential exposures to airborne asbestos because of mining activities in the area. The study by Wigle (1977) compared the mortality rates for various causes in individuals ingesting $\leq 10^9$ f/ℓ of chrysotile asbestos in water compared with those drinking what was thought to be much lower concentrations of asbestos. Excess cancers of the stomach and lung in males and of the pancreas in females were observed in the two municipalities with extremely high exposures. However, the male mortality may have been from occupational exposure to asbestos. Toft et al. (1981) compared the age-adjusted mortality rates for the communities of Sherbrooke and Thetford Mines with 52 comparison localities believed to have considerably lower asbestos exposures. Stomach and lung cancers were elevated in men at Thetford Mines, presumably from occupational exposures; no elevated risks were found at Sherbrooke, a municipality with high fiber concentrations in water. The population is relatively small and the comparison analysis is of very low power.

A series of studies have been conducted of the cancer incidence in the San Francisco Bay area, part of which is served by water systems containing concentrations of chrysotile asbestos ≤36 million fibers/ℓ. The first published report of this research (Kanarek et al., 1980) compared cancer incidence in low (16,000-32,000 f/ℓ), medium (330,000-4,100,000 f/ℓ) and high 5,400,000-36,000,000 f/ℓ) fiber groups of census tracts. Correlation coefficients significant at the $p<0.01$ level were found between chrysotile asbestos water concentrations and white male lung cancer, white female gallbladder and pancreatic cancer, and peritoneal cancer in both sexes. Weaker correlations ($0.01<p\leq 0.05$) were found between asbestos levels and female esophagus, pleura and kidney cancer, as well as stomach cancer in both sexes. A later follow-up (Conforti et al., 1981) extended the observations through 1974 and found a correlation between chrysotile asbestos

content and white male cancers of the digestive tract, esophagus, stomach and pancreas. White female cancers of the esophagus, stomach, digestive-related organs and pancreas were also elevated. The associations appeared to be independent of income, education, asbestos occupation, marital status and population mobility. The variables tested, however, were group census data on socioeconomic status and for occupation, the variable was number of construction, electrical and textile workers, as these trades were considered to have a possible occupational exposure to asbestos. A later analysis of Conforti (1983) considered population density as an independent variable and found that consideration of this variable led to slightly more significance for the asbestos regression coefficients that indicated a positive association between ingested chrysotile asbestos and some cancer sites. However, it was the conclusion of the author that population density had little effect on the observation of an association between ingested asbestos and cancer (Conforti, 1983).

One interesting analysis of the correlation between digestive system cancer and asbestos concentrations is that of Tarter et al. (1983). They found that within San Francisco, in the high asbestos exposure areas, there may be two subpopulations, each having a different risk or different risks of GI cancer. The origin of this bimodal response is unclear.

A study by Polissar et al. (1982) found no association between high concentrations of chrysotile asbestos ($\leq$200 million f/ℓ) in drinking water of Puget Sound, Washington and cancer at various digestive sites. However, only 78,000 individuals were served by a water system with such levels. In their initial study, cancer incidence and mortality data for individuals drinking water with high asbestos content were compared with populations having much lower exposures (~7x10^6 f/ℓ) in other areas. Odds ratios for tumors of the small intestine were consistently elevated in both sexes, as were those for neoplasms of the thyroid, eye, testes and prostate in males. Inasmuch as 332 different odds ratios were calculated, the possibility that these significant elevations occurred by chance is high. The authors did not attribute any of the increases to the asbestos in community water supplies. Subsequently, a case-control study was conducted by Polissar et al. (1983, 1984). Through the western Washington population-based tumor registry, 382 cases were identified as having cancer of the buccal cavity, pharynx, respiratory system, digestive system, bladder or kidney. The control group consisted of 462 individuals. Interviews were conducted with all individuals and validated by secondary sources along with other methods. Estimates of exposure were made based upon information obtained through the interviews. The authors conclude that there was no convincing evidence for cancer risk from ingested asbestos. The exposure between the cases and controls were found to be similar. Of 84 dependent estimates of risk by sex, cancer site and exposure, 63 were found to produce a protective effect and 21 were found to increase risk. The only sites where results might be considered slightly suggestive are male pharynx and male stomach. However, this result is considered to be spurious based on the number of tests made and because the female risks at the same two sites indicate a protective effect.

Millette et al. (1983) studied cancer mortality for the populations in 40 census tracts of Escambia County, FL that had been receiving drinking water through AC pipes [chrysotile (DNR) and amphibole (DNR)] for $\leq$40 years (1-10x10^6 f/ℓ). Cancer mortality data from these 40 census tracts were compared with data from other tracts where AC pipe was not in use. No statistical association was observed between cancer deaths and the use of AC pipe. This is consistent with the finding of Harrington et al. (1978) who studied the use of AC pipe (chrysotile; $\leq 0.7\times10^6$ f/ℓ) in public potable water supplies and GI cancer incidence in Connecticut for the period 1935-1973. Meigs et al. (1980) also studied AC pipe and cancer incidence in Connecticut but for the period 1955-1974. The only association noted was a positive association between male pancreatic cancer and ingested asbestos. Both Connecticut studies investigated age-adjusted, sex-specific incidence data for stomach, colon and rectal cancers.

Three additional studies included in this chapter are reviewed by Marsh (1983). Tarter (1981) offered supportive evidence to the observations by Kanarek et al. (1980) and Conforti et al. (1981) for the San Francisco Bay area. Tarter (1981) observed an increase in all GI cancer sites combined for both males and females. Sadler et al. (1981) investigated associations between cancer incidence and the use of AC pipe (chrysotile; DNR; #fNR) in Utah. The only positive associations found were for female gallbladder cancer and male kidney cancer and leukemia/aleukemia. Finally, Severson (1979) investigated cancer mortality in the Puget Sound area. No positive associations were found between cancer and mortality and asbestos exposure (chrysotile: DNR; $7.3\text{-}206.5\times10^6$ f/ℓ) in drinking water.

In a detailed review of 13 of these studies (Mason et al., 1974; Levy at al., 1976; Sigurdson et al., 1981; Harrington et al., 1978; Meigs et al., 1980; Wigle, 1977; Toft et al., 1981; Kanarek et al., 1980; Conforti et al., 1981; Tarter, 1981; Sadler et al., 1981; Severson, 1979; Polissar et al., 1982) Marsh (1983) includes a lengthy discussion of their limitations. A section of his excellent discussion is included here.

The large variability in findings evident among the studies is matched by a considerable discrepancy in results for males and females within the 13 studies. Several factors might explain, at least in part, the internal and external inconsistencies in results...the discrepant results may be due to differences in characteristics of asbestos exposure in the various study populations. These differences are summarized in Table VI-4. The relatively low number of positive associations found in Utah and Connecticut could be due to the low concentrations of asbestos in the drinking water or to the relatively short duration of community exposure in several study subareas. The virtual absence of positive findings in the (Sigurdson et al., 1981) Duluth study could also be due to relatively short duration of exposures as well as the amphibole fiber, which is fundamentally different from the chrysotile fibers found in the remaining study areas. By utilizing the differences in exposure characteristics, the three study areas associated with long duration of exposures (>40 years) to chrysotile asbestos can be roughly ranked according to the concentration of fibers in their water systems. However, the resulting ranking, Bay Area (lowest), Puget Sound (intermediate), and Quebec (highest), does not appear to be related to the pattern of associations shown in Tables VI-2 and VI-3.

In addition to duration and intensity, it is also likely that other exposure factors, such as the characteristics of asbestos pipe used, the concentration of other possibly carcinogenic contaminants of water, and certain physical properties of asbestos fiber (e.g., length), vary among and within the six study areas.

As a second major factor, the different study designs employed in the various areas, coupled with the disparity in their underlying strengths and weaknesses, most likely also contributed to the observed variability in results. The most important methodologic weaknesses and limitations ascertained from the individual reviews are summarized in Table VI-5. The weaknesses are listed in approximate decreasing order of importance relative to their potential impact on the credibility and definitiveness of the findings.

TABLE VI-4

Characteristics of Asbestos Exposures in Drinking Water in Various Study Populations[a]

Characteristic	Duluth, MN	Connecticut	Quebec	Bay Area, CA	Utah	Puget Sound, WA
Type of asbestos	amosite	chrysotile	chrysotile	chrysotile	chrysotile	chrysotile
Number of fibers/ℓ	1.0-30.0x10^6	BDL[b]-0.7x10^6	1.1-1300x10^6	0.025-36x10^6	NA[c]	7.3-206.5x10^6
Population exposed	100,000	576,800	420,000	3,000,000	24,000	200,000
Maximum duration of exposure, year	15-20	23-44	>50	>40	20-30	>40

[a] Source: Adapted from Marsh, 1983

[b] BDL = Below detectable limit

[c] NA = Data not available

TABLE VI-5

Summary of Methodologic Weaknesses and Limitations Associated with Various Studies of Ingested Asbestos[a,b]

Weakness/limitation[c]	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA		Total Across Studies
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Ecologic study design	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Insufficient latency period	*	*	*	-	-	-		-	-	-	*	-	-	4
Death certificate data	*	-	-	-	-	*	*	-	-	-	-	-	-	3
Duration and/or intensity of exposure low	*	*	*	*	*	-	-	-	-	-	*	-	-	6
Uncontrolled confoupding														
Race	-	*	*	*	*	*	*	-	-	*	*	*	*	10
Sex	-	-	-	-	-	-	-	-	-	*	-	-	-	1
Occupation	*	*	*	*	*	*	*	-	-	*	*	*	-	10
Socioeconomic status	*	*	*	*	-	*	*	-	-	*	-	-		7
Population density	*	*	*	-	-	*	*	*	*	*	-	*		10
Ethnicity	*	*	*	*	*	*	*	-	-	*	*	*		11
In/out migration	*	*	*	*	*	*	*	-	-	*	-	-	-	8
Personal habits	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Absence (or incomplete) data on dose-response	*	*	*	*	*	-	-	-	-	-	*	*	*	8
Multiple comparisons problem	*	*	*	*	*	*	*	*	*	-	*	*	*	12
Insensitivity of summary statistics	*	*	*	*	*	-	-	*	*	*	-	*	*	10
Absence of historical asbestos exposure data	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Use of at least one questionable statistical procedure	-	*	-	-	*	-	-	*	*	-	-	-	-	4
Total	14	15	14	12	12	11	11	7	7	11	10	10	9	

[a] Source: Adapted from Marsh, 1983

[b] Legend asterisk (*) indicates presence of characteristic; minus (-) indicates absence of characteristic

[c] In approximate decreasing order of relative impact on definitiveness of study results

1. Mason et al., 1974
2. Levy et al., 1976
3. Sigurdson et al., 1981
4. Harrington et al., 1978
5. Meigs et al., 1980
6. Wigle, 1977
7. Toft et al., 1981
8. Kanarek et al., 1980
9. Conforti et al., 1981
10. Tarter, 1981
11. Sadler et al., 1981
12. Severson, 1979
13. Polissar et al., 1982

By far the most serious limitation of all the studies conducted to date is that they are ecological or, more specifically, geographic correlation studies by design. This drawback alone does not permit a definitive conclusion to be made from any of the studies of the possible adverse health effects of ingested asbestos. The major drawback of ecological analysis for testing etiologic hypotheses is the potential [illegible] substantial bias in effect estimation. This problem, known as the "ecological fallacy," results from making a causal inference about individual phenomena on the bias of observations of groups. Theoretically, the bias resulting from ecological analysis can make an association appear stronger or weaker than it is at an individual level; however, in practice, this bias ordinarily exaggerates the magnitude of a true association, if one exists (Langbein and Lichtman, 1978; Duncan et al., 1961; Valkonen, 1969). Ecologic study bias can be minimized, for example, through the judicious application of ecologic regression techniques. Such techniques were employed, at least in part, in the Connecticut study of Meigs et al. (1980), the three Bay Area studies, and the two Puget Sound studies. However, the overall variability in results does not appear to be any less among or within these six studies compared to the remaining seven, which did not incorporate more refined ecologic analyses.

Much of the bias inherent in ecologic analysis results from the inability to control for confounding factors at the individual level. Table VI-5 shows that most of the studies reviewed did not directly control for confounding factors even at the group level. Notable exceptions are the Bay Area studies of Kanarek et al. (1980) and Conforti et al. (1981) and the two Puget Sound studies, which employed relatively more sophisticated multivariate statistical analyses as an attempt to control for confounding at the group level. Only one study to date, that of Polissar et al. (1982), attempted to collect data on a confounding variable at the individual level; however, since this was done only for cancer cases and not controls, it was not possible to analyze the data on a more sensitive and reliable case-control basis.

Occupation was a particularly important confounding variable in the studies conducted in Quebec, the Bay Area, and Connecticut, since a substantial number of males are employed in the various asbestos-related industries within these areas. The confounding effects of occupation are particularly evident in the two Quebec studies, where positive associations for lung and stomach cancer were consistently confined to males.

Misclassification of asbestos exposures is another serious limitation of all the studies conducted to date. This misclassification results from several factors including: the basic ecologic design, which assigns specific exposures to an entire geographic area; tenuous assumptions regarding the extent of asbestos contamination from asbestos pipes; the lack of any reliable historical asbestos exposure data; and the in/out and daily mobility of the study populations.

It is also likely that many of the associations found among the 13 studies are simply chance occurrences arising from the large number of statistical comparisons that were generally made. Whenever a large number of significance tests are performed at a constant significance level, a certain number of tests will be significant by chance alone and the actual significance levels must be higher than those reported by the authors. Among the 13 studies reviewed, the number of separate statistical comparisons reported ranged from 33 to 336 with an average of 193. Therefore, at a 5% level of significance, the number of positive findings expected due to chance alone would range from approximately 2 to 17 with an average across the 13 studies of about 10. In other statistical terms, the probability that at least one of the n independent comparisons was due to chance alone ranged from 0.81 in a study reporting about 30 comparisons to virtual certainty in studies reporting 100 or more comparisons. (At the 5% level of significance, the probability of falsely claiming statistical significance in at least one of n independent comparisons is $1-0.95^n$.)

Marsh (1983) also conducted a probability analysis of eight independent studies (Mason et al., 1974; Sigurdson et al., 1981; Meigs et al., 1980; Wigle, 1977; Toft et al., 1981; Conforti et al., 1981; Sadler et al., 1981; Polissar et al., 1982) attempting to associate increased cancer risk with asbestos exposure. He considered whether the observed positive associations in males and females for neoplasms at various GI sites were likely to have been generated by chance, and found that those of the esophagus, stomach, pancreas and prostate may have a biological basis related to ingested asbestos. Marsh treated each independent study equally, even though studies of Connecticut were severely limited by the low asbestos concentrations in the study area, and the study of Utah was limited by a very small exposed population. Were these studies to be excluded from his analysis, the strength of positive findings would be increased.

In a review of Table VI-2 it can be seen, as was demonstrated analytically by Marsh (1983), that the possibility of an elevated risk of cancer of the stomach and pancreas must be considered as possibly associated with ingestion of asbestos in water. The stomach is an obvious site for concern as this cancer rate has been shown to be elevated in several studies of occupationally-exposed workers. Cancer of the pancreas has not been directly implicated as a site of elevated cancer risk from exposure to asbestos through inhalation. However, a large number of peritoneal mesotheliomas have been misclassified as cancers of the pancreas (Selikoff et al., 1979) and, in the absence of complete pathological review, an increase in pancreatic cancer may be the result of an increase in peritoneal mesothelioma. The finding of an elevated cancer risk of the peritoneum in San Francisco and, perhaps in Duluth, also is suggestive.

All of the studies discussed, with the exception of Polissar et al. (1983, 1984) are limited because of their ecological design. Group data are utilized for exposure estimates and for possible confounding variables. One of the most serious of confounding factors is that of possible occupational exposure to asbestos. Nicholson et al. (1979) estimated that 20 million individuals in the United States may have had employment in an industry with possible exposure to asbestos. More than 4 million are known to have had previous shipyard employment where asbestos risks are high. Studies by Blot et al. (1978) suggested that employment in a shipyard for as short as 2-3 years increases the risk of lung cancer by 60%. A study by Puntoni et al. (1979) demonstrated an elevated risk of lung cancer (O/E=2.24), cancer of the stomach (O/E=1.36) and cancer of the colon (O/E=1.81). The San Francisco Bay area was one of the most important ship-building regions of the United States, and many current residents would be expected to have had past employment in one of the Bay areas yards. Further, the SEER Program indicates that the mesothelioma mortality experience in the Bay area is one of the highest in the United States (NAS, 1984). The possible confounding effect of occupational exposures requires that a definitive analysis of cancer risk in the Bay area explicitly take into account occupation on an individual basis. This would suggest a case control study of cancers of the esophagus, stomach, pancreas and perhaps colon and rectum. The study design should be prospective and incorporate in the protocol the interviewing of individuals at the time of diagnosis, so that occupational, residential and other relevant histories can be taken from the individual in question rather than from relatives. It should also include a pathological review of all tissue material available on pancreatic cancers in order to ascertain whether misclassification of mesothelioma has occurred.

Doll (1985) has reviewed health effects associated with exposure to asbestos and noted that peritoneal mesothelioma may be misdiagnosed as GI cancer. Newhouse and Wagner (1969) obtained necropsy (autopsy) reports for 158 asbestos factory workers (84 contained histology) and compared the cause of death with that reported on the death certificate. Using necropsy reports reduced the GI cancers by half and increased the mesotheliomas 4-fold. Since that time, mesothelioma has come to be a recognized diagnosis. Selikoff et al. (1979) reported no change in the GI cancer rate when underlying cause of death by "best evidence" was compared with the death certificate for 2771 deaths. Doll (1985) concluded that GI cancers are not partic- ularly likely to be caused by asbestos exposure.

High-Risk Subpopulations

Hypersusceptible individuals have not been defined for ingested exposures to mineral fibers. It is well known that smokers exposed to asbestos dusts from inhalation are at a higher risk of developing lung cancer than are nonsmokers with similar exposures (Hammond et al., 1979). This phenomenon has not been demonstrated to also apply to the ingestion of asbestos. Since it is theorized that ingested asbestos may result in increased cancers of the digestive system, one would expect that persons with pre-existing diseases, ailments or risk factors associated with the digestive system would be more susceptible to the carcinogenic potential of ingested asbestos. However, no such data were found in the available literature. This is an area requiring further research.

Summary

Acute exposures to ingested asbestos fibers in humans have resulted in the detection of fibers in body fluids that has not been associated with specific health effects. Chronic exposures have not resulted in nonmalignant effects; however, several studies have been performed to investigate the carcinogenic potential of chronic exposure to ingested asbestos on human populations. The results of these studies are summarized in Tables VI-2 and VI-3.

The possibility of an elevated risk of cancer of the stomach and pancreas must be considered as suggestively associated with ingestion of asbestos in water and thus, not inconsistent with a hypothesis that ingested asbestos by the drinking water route might have tumor carcinogenic potential. The strong evidence of GI tract cancer resulting from inhalation exposure and the assumed swallowing of inhaled fibers as the ingestion mode, clearly demonstrates that under certain conditions, asbestos has a definite potential for human carcinogenicity by ingestion. The question of dose-response patterns and quantitative risk analysis is a separate and distinct topic.

VII. MECHANISMS OF TOXICITY

Investigation of the mechanism of ingested asbestos toxicity has concentrated on the effects of asbestos in the gut. Research has been conducted in vivo and in vitro. Studies discussed in this chapter are listed and summarized in Table VII-1. A discussion of asbestos toxicity associated with fiber size and type is contained in the Appendix.

Toxicity

Jacobs et al. (1977) reported changes in the DNA, RNA, protein and some enzyme activities in the small intestine mucosal lining cells and gut lumen, induced by maintaining rats on a diet containing UICC Rhodesian chrysotile asbestos (DNR). Test groups of six rats were fed chrysotile asbestos at 0.5 mg or 50 mg asbestos/day (#fNR) both pretreated with cigarette smoke and in the absence of cigarette smoke for a period of 10 months. Control groups (also six rats) received either commercially available rat pellets or rat pellets pretreated with cigarette smoke.

Results of this study reveal that persistent ingestion of asbestos in the diet induced some changes in the gut mucosal lining cells, but greater alterations were detectable in the levels of macromolecules in the lumen of the small intestine. The levels of RNA in the lumen were significantly lower and DNA significantly higher in all groups of animals ingesting asbestos (irresponsive of cigarette smoke pretreatment) compared with control animals. These alterations of macromolecules in the lumen were judged to be consistent with a mineral-induced cytotoxicity. Most intracellular enzyme levels were consistently, but not significantly, elevated in

TABLE VII-1

Studies Relevant to Mechanisms of Asbestos Toxicity

Species/Test System	Route of Exposure/ Vehicle	Type of Asbestos and Dimensions	Dose and Duration	Results	Reference
TOXICITY					
Rat (male, MRC hooded) (6/dose group) isolated small intestine	Ingestion/ feed	UICC Rhodesian chrysotile (DNR)	0.0, 0.5 and 50 mg/ day (# FNR) for 10 months	Changes in the gut mucosal lining cells compared with controls at both asbestos doses. The lumen of the small intestine had significantly increased mean DNA and significantly decreased mean RNA levels. Enzyme activity was significantly elevated in the lumen. B-glucuronidase activity was elevated in mucosal cells.	Jacobs et al., 1977
Rat (male, MRC hooded) (6/dose group for asbestos exposed)	Ingestion/ feed	UICC Rhodesian chrysotile (DNR)	0 and 50 mg/day (# FNR) for 1 week or 5-15 months	Asbestos interfered with DNA metabolism in the GI tract. A significant increase in the incorporation of [^{3}H]-thymidine into DNA was observed in asbestos-exposed animals compared with controls.	Jacobs et al., 1978b
Rat (MRC hooded, sex NR) isolated small intestine	Ingestion/ feed	Chrysotile (DNR)	0 and 50 mg/day (# FNR) for 10 weeks	Statistically significant lower levels of radiolabeled glucose (^{3}[H]-sucrose) and its radioactive degradaton products in perfused isolated small intestine of asbestos-fed rats compared with controls suggests that the cellular energized carrier mechanism that transports this sugar is impaired by cytotoxic action of asbestos on mucosal cells of the small intestine.	Jacobs and Richards, 1980
Rat (F344) isolated colon tissue	Ingestion/ feed	UICC Canadian Chrysotile B (DNR)	A 10% asbestos (# FNR) in diet (36 animals) 10% nonnutritive cellulose in diet (fiber control) (30 animals); a standard lab diet (vehicle control) (6 animals) for 24 months	Cyclic-AMP levels in isolated colon tissues were significantly lower in asbestos-fed animals compared with controls.	Donham et al., 1980

TABLE VII-1 (cont.)

Species/Test Material	Route of Exposure/ Vehicle	Type of Asbestos and Dimensions	Dose and Duration	Results	Reference
CELLULAR EFFECTS					
Human embryonic intestine-derived (I-407) epithelial cells	*In vitro*	UICC Canadian Chrysotile B, UICC Crocidolite, UICC Amosite	$5 \times 10^{-5}\%$ $10^{-3}\%$ solution for 0-7 days	The order of cytotoxicity was chrysotile > amosite > crocidolite.	Reiss et al., 1980a
Rat liver-derived (ARL-6) epithelial cells	*In vitro*	UICC Canadian Chrysotile B, UICC Crocidolite, UICC Amosite	$5 \times 10^{-5}\%$ $10^{-3}\%$ solution for 0-7 days	All three asbestos types were more cytotoxic to I-407 than to rat ARL-6 cells. The order of cytotoxicity was chrysotile > amosite > crocidolite.	Reiss et al., 1980a
Mouse colon-derived epithelial-like (MCE-1) cells	*In vitro*	UICC Canadian Chrysotile B, UICC Crocidolite, UICC Amosite	$5 \times 10^{-5}\%$ $10^{-3}\%$ solution for 0-7 days	Mouse MCE-1 cells were more resistant than human I-407 cells. No change in cytotoxicity of fibers leached in sterile deionized water. Leaching in hydrochloric acid decreased the cytotoxicity of chrysotile and slightly increased the cytotoxicity of amosite and crocidolite.	Reiss et al., 1980a
P388D1 macrophage-like cells	*In vitro*	UICC Amosite, UICC Chrysotile B	10, 50 or 100 μg/cm² up to 72 hours	Fiber-induced cytotoxicity to the P388D1 cells has been demonstrated to parallel the probability that the fiber will induce a pleural sarcoma (mesothelioma) in rats. Effect is independent of the chemical nature of the fiber and correlates best with fibers 8 μm in length and with diameters in the range of 0.5-1.0 μm (Stanton Hypothesis).	Lipkin, 1980
Human red blood cells	*In vitro*	UICC Chrysotile (avg. length <5 μm) UICC Crocidolite (avg. legnth <4 μm)	chrysotile, 0.1-5 mg/mℓ (# FNR) for up to 60 minutes; crocidolite, 1.0 mg/mℓ (# FNR) for up to 60 minutes	Hemolysis resulted from an increase in membrane permeability and not from rupture of RBCs. The fibers extract and adsorb lipids. Percent hemolysis varied directly with the ratio of fiber surface area to RBC surface area.	Jaurand et al., 1979
SYNERGISTIC EFFECTS					
Rat liver microsomes	*In vitro*	UICC Canadian Chrysotile (DNR), UICC Anthophyllite (DNR)	# FNR, for up to 30 minutes	Particulate-enhanced availability of BaP to rat liver microsomes when BaP is adsorbed to asbestos.	Lakowicz and Bevan, 1980

TABLE VII-1 (cont.)

Species/Test Material	Route of Exposure/ Vehicle	Type of Asbestos and Dimensions	Dose and Duration	Results	Reference
Rat or rabbit liver microsomes	*In vitro*	UICC Crocipolite (DNR), UICC Canadian Chrysotile B (DNR), UICC Amosite (DNR), UICC Anthophyllite (DNR)	# FNR	Rapid transport of BaP into the membrane of rat liver microsomes and impaired BaP metabolism from aryl hydrocarbon hydroxylase inhibition.	Kandaswami and O'Brien, 1979
CBA mice (3-week-old, both sexes)	i.p. in physiological saline	UICC Crocidolite finely ground	5 mg/mℓ (# FNR); 5 μg/mℓ (# FNR) plus 10^5 FFU/mℓ of Moloney murine sarcoma virus; virus control; saline control; all single dose	Incidence of animals with palpable tumors observed within 100 days; 44/61 (72.1%) for asbestos + virus 50% lethal; 0/60 asbestos only; 1/59 virus control; 0/98 saline control. The neoplasms appeared to be anaplastic sarcoma and were mostly confined to the serosal surface of the abdominal cavity.	Kanazawa et al., 1979

*Type of asbestos and dimensions (dimensions dependent on method of preparation):

from Langer et al. (1974) (ultrasonically dispersed in water):

	Modal Length (μm)	Modal Width (μm)
Crocidolite UICC (S. African)	0.6	0.13
Amosite UICC (S. African)	1.4	0.14
Tremolite (Montana)	5.1	0.17
Anthrophyllite UICC (Finnish)	5.1	0.18

from NTP (1985):

	Range of Mean (μm)	Range of Mean (μm)
Chrysotile, NIEHS short range (SR), (California, Union Carbide)	0.66	0.059
Chrysotile, NIEHS intermediate range (IR), (Quebec, Johns Manville-Plastobest-20)	0.82	0.089

from Atkinson (cited in Harington et al., 1975, p. 306)

	Range of Mean (μm)	Range of Mean (μm)
Chrysotile (Quebec)	1000-2000	0.030-0.038

DNR = Dimensions not reported; # FNR = number of fibers not reported; NR = not reported animals maintained on asbestos diets. Enzyme activities within the lumen were significantly higher in exposed animals compared with controls.

In a follow-up study, Jacobs et al. (1978b) reported a significant increase in the incorporation of [^{3}H]-thymidine into DNA in the small intestine mucosa, colon, rectum, stomach and spleen of rats that had ingested 50 mg/day (#fNR) UICC Rhodesian chrysotile (DNR) chrysotile in both the short- (1 week) and long-term (5-15 months) experiments. This work provides supporting evidence that ingestion of chrysotile asbestos interferes with DNA metabolism in rat tissues in the GI tract and other body organs. In more recent work, Jacobs and Richards (1980) monitored the distribution of [^{3}H]-sucrose and its radiolabeled degradation products in isolated perfused small intestine loops of rats that had previously ingested 50 mg/day (#fNR) chrysotile (DNR) for 10 weeks. They discovered lower levels of radiolabeled glucose in these rats compared with controls suggesting that active transport of glucose across the intestinal membrane was impaired.

Donham et al. (1980) studied the effects of ingested UICC Canadian chrysotile B asbestos (DNR) on the colon of male weanling F344 rats. Based on results of preliminary experimentation, the dosage was established at 10% by weight (#fNR) of a standard laboratory diet. Animals received this diet for 24 months. Thirty-six animals comprised the test group; there were also 30 control rats fed 10% nonnutritive cellulose and a group of 6 controls was fed normal laboratory chow. The study was terminated at 33 months. The mean concentration of cyclic AMP in isolated colon tissue of asbestos-fed animals (132 picomoles/mg DNA) was lower than the mean for either the cellulose control animals (388 picomoles/mg DNA) or the normal laboratory diet control animals (299 picomoles/mg DNA). This difference was statistically significant for the asbestos-fed animals compared with the normal laboratory diet animals indicating a serious cell regulator defect related to asbestos ingestion.

Cellular Effects

In vitro tests with asbestos-induced cellular responses and their possible relationship to neoplasia in GI and respiratory epithelium have been reviewed by both Mossman (1983) and Daniel (1983). Asbestos fibers interact with mucosal cells of both the GI and respiratory tract. Their composition and cytotoxicity are modified by acidity and coating with natural secretions. The biological activity of various types of asbestos is determined by surface charge, crystallization and dimensional characteristics. These factors influence the adsorption of natural secretions and serum components to fibers which, in turn, ameliorates cytotoxicity. In reviewing studies of such interactions, Mossman (1983) concluded that asbestos fibers appear to be epigenetic carcinogens and that the role of asbestos fibers in carcinogenicity in respiratory epithelium can be compared with that of classical tumor promoters. This is supported by the fact that various types of asbestos do not cause single-strand breakage of DNA in human and hamster respiratory epithelial cells. Also, unless combined with PAH, UICC crocidolite asbestos (DNR; #fNR) is not carcinogenic in hamster tracheal implants (Mossman and Craighead, 1978) nor in rat tracheal organ cultures *in vitro* (Mossman and Craighead, 1981). Daniel (1983) concludes that while asbestos fibers are clastogenic to cultured rodent cells, there is little other evidence for genotoxicity of fibers. Thus, as stated by Daniel (1983), although fibers may act at the stage of tumor initiation (gene toxicity) by means of a clastogenic event, it may be more reasonable to look at other mechanisms such as cocarcinogenesis or promotion for the oncogenic potential of these mechanisms.

Reiss et al. (1980a) demonstrated the cytotoxic action of asbestos on various mammalian cell lines *in vitro*. UICC amosite, UICC crocidolite and UICC Canadian chrysotile B asbestos were assayed for their cytotoxicity using embryonic human intestine-derived (I-407), adult rat liver-derived (ARL-6) epithelial cells and mouse colon-derived epithelial-like (MCE-1) cells in culture. The order of cytotoxicity was chrysotile > amosite > crocidolite. All three types of asbestos were more toxic to human I-407 cells than to either type of animal cells. Mouse MCE-1 cells were similar to rat ARL-6 cells in response to chrysotile and amosite but more sensitive to crocidolite.

Other recent evidence is available demonstrating the effects of asbestos on cellular membranes. Jaurand et al. (1979) investigated the effects of exposure of human erythrocytes (red blood cells) to asbestos fibers. Asbestos fibers [UICC chrysotile (average length <5 μm) and UICC crocidolite (average length <4 μm)] and erythrocytes were pre-incubated separately for 10 minutes at 37°C. For time periods up to 60 minutes, 1 mℓ (#fNR) of each suspension was mixed together and incubated at 37°C. At the end of the exposure period samples were centrifuged 10 minutes at 1200 x g and optical density was determined at 540 nm. Results were expressed as percent of hemolysis. Complete hemolysis was obtained by addition of 0.2% (v/v) Triton X-100 to the erythrocyte suspension.

Examination of the kinetics of hemolysis in an isotonic medium with various concentrations of red blood cells and fibers revealed that maximal hemolysis depended on the relative concentrations of chrysotile and erythrocytes, not on the absolute concentration. A 10-fold increase in the absolute concentrations of each (e.g., 0.5 mg/mℓ chrysotile and 0.5% red blood cells up to 5 mg/mℓ chrysotile and 5% red blood cells) resulted in the same kinetics and final level of hemolysis. These results indicate that hemolysis of erythrocytes by chrysotile is a self-inhibiting process. Microscopic studies showed that the effect of asbestos on red blood cells is not a rupture of the cells but a progressive increase in membrane permeability. The cells lose hemoglobin, gradually become ghosts, and subsequently disappear into the bundles of fibers. In this study Jaurand et al. (1979) demonstrated a direct relationship between maximal hemolysis and the ratio of the surface areas of chrysotile and red blood cells in the medium. They assumed that the inhibition of hemolysis by asbestos fibers is attributable to binding of red cell membrane components, either lipids or protein, or both. This assumption was verified by preincubating asbestos fibers with red cell ghosts or liposomes made either of dipalmitoyl phosphatidylcholine alone or a mixture of lipids. This preincubation step prevented subsequent hemolysis of red cells. Therefore, it was concluded that the effect of chrysotile on red cells is at least partly, if not completely, attributable to lipid extraction and adsorption onto the fibers.

Other studies have demonstrated effects of asbestos on cellular membranes. Newman et al. (1980) reported that various types of asbestos affect surface membrane glycolipids and glycoproteins of Syrian hamster embryo cells, possibly increasing membrane permeability and allowing other mutagens into the cell (see Chapter VI). The effect was greatest with crocidolite (DNR, #fNR) followed by chrysotile (intermediate) (DNR, #fNR) and then amosite (DNR, #fNR).

Synergistic Effects

The effects of asbestos fibers on cellular membrane permeability has led some investigators to explore possible synergistic effects between asbestos and other substances.

Some studies have demonstrated effects of several types of asbestos on B[a]P transport and metabolism, especially transfer of the carcinogen from the surface of particulate material to rat liver microsomes, microsomal membranes and lipid micelles (Lakowicz and Bevan, 1980; Kadaswami and O'Brien, 1980; McLemore et al., 1979; Hart et al., 1980; Brown et al., 1983; Mossman and Craighead, 1981). Asbestos mediates a rapid transport of B[a]P across cellular membranes and this enhanced availability may be a significant factor in the cocarcinogenesis between particulate material and PAHs. Asbestos appears to alter B[a]P metabolism and activity of aryl hydrocarbon hydroxylase. The relevance of these factors to ingested asbestos has not been established.

Some evidence of synergistic effects of asbestos on other agents was provided by Kanazawa et al. (1979). They administered 5 μg/mℓ (#fNR) UICC crocidolite asbestos (DNR) plus 10^5 FFU/mℓ Moloney murine sarcoma virus in physiological saline i.p. in CBA mice and observed for 100 days.

Palpable intraperitoneal tumors were observed in 72.1% of mice receiving asbestos and virus while 1/59 mice developed similar tumors with virus alone; no tumors were reported in mice receiving asbestos only or in saline controls.

Summary

The elucidation of the mechanism of toxicity of ingested asbestos in humans is based upon extrapolation from animal or *in vitro* research. Asbestos has been demonstrated to interfere with DNA metabolism in rat tissues of the GI tract and other organs. In addition, impaired active transport of glucose across membranes and other cytotoxic effects have been associated with asbestos exposure. Specifically, chrysotile exposure has resulted in the hemolysis of erythrocytes. The effect of chrysotile on red blood cells may be attributed to lipid extraction and adsorption onto fibers.

Asbestos may act as a cocarcinogen with B[a]P and Maloney murine sarcoma virus. Asbestos mediates transport of B[a]P across cell membranes and may alter B[a]P metabolism. A greater number of tumors were seen in animals receiving asbestos + virus than seen in animals receiving asbestos or virus alone. Additional work is needed in this area.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Introduction

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{[\text{Uncertainty Factor(s)} \times \text{Modifying Factor}]} = \underline{\quad\quad} \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner, the U.S. EPA (1988) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]
- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]
- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]
- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{(\text{RfD}) \times (\text{Body weight in kg})}{\text{Drinking Water Volume in } \ell\text{/day}} = \_\_\_\_ \text{ mg}/\ell$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{bw})}{(\text{UF}) \times (\_\_\_ \ \ell\text{/day})} = \_\_\_\_ \text{ mg}/\ell$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Very few studies were found in the literature that investigated toxic effects following the ingestion of asbestos fibers. However, the limited data suggest that the general toxicity following the ingestion of asbestos is minimal in both animals and humans, with no specific target organ defined. This is in sharp contrast to the range of noncarcinogenic toxic effects seen following exposure by inhalation to asbestos particles; the most severe being asbestosis. The only noncarcinogenic toxic effects reported in animals following ingestion were changes in the muscosal lining cells of the ileum along with changes in the colon, rectum and small intestine of rats given either 0.5 or 50 mg/day (#fNR) UICC Rhodesian chrysotile asbestos (DNR) for 1 week or 14 months (Jacobs et al., 1978a). Human studies are limited to the detection of fibers in body fluids, which has not been associated with specific health effects. Other studies were performed on in vivo and in vitro test systems.

Quantification of Noncarcinogenic Effects

It is, therefore, evident that there are insufficient toxicological data on which to base a recommendation for a 1-day (child) or 10-day HA (child) for asbestos. In addition, it is also considered prudent not to derive longer-term HAs or a DWEL, since the endpoint toxicity from inhaled asbestos exposure is carcinogenicity and the latent period for the cancer to appear from an occupational exposure of asbestos is in the magnitude of ≥20 years.

Carcinogenic Effects

Data developed since the early 1970s, from large population studies with long follow-up, have added to our knowledge of asbestos disease. Lung cancer and mesothelioma are the most importatnt asbestos-related causes of death among inhalation exposed individuals. Gastrointestinal cancers are also increased in most studies of occupationally (inhalation) exposed workers. Cancers at other sites (larynx, kidney, ovary) have also been shown to be associated with asbestos exposure in some studies, but the degree of excess risk and the strength of the association are less for these and the GI cancers than for lung cancer or mesothelioma. The International Agency for Research on Cancer (IARC, 1982) lists asbestos as a Group 1 carcinogen, meaning that exposure to asbestos is carcinogenic to humans. U.S. EPA's carcinogen guidelines categorize asbestos as Group A, human carcinogen (U.S. EPA, 1986b). Animal inhalation studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma with only limited differences in carcinogenic potency. Implantation and injection studies show that fiber dimensionality, not chemistry, is the most important factor in fiber-induced carcinogenicity. Long (>4 μm) and thin (<1 μm) fibers are the most carcinogenic at a cancer-inducible site. However, the size dependence of the deposition and migration of fibers also affects their carcinogenic activity in humans.

The qualitative inference that asbestos would be a human carcinogen by ingestion exposure is demonstrated by several types of data. The observation of GI tract cancer in humans occupationally exposed is quite strong, there being 20/23 studies with an elevated GI cancer incidence, with 10 of the 23 being significant at the 0.05 level. While there is debate regarding the dose mechanism and regime involved and the possibility of some misdiagnosis of cancer, it is difficult to accept that these issues effectively discount the observations such that a strong qualitative association no longer exists. Secondly, epidemiologic studies specifically focused upon ingestion exposure to asbestos have demonstrated some associations between cancers of the lung, stomach and pancreas. This conclusion is based on a critical review of 14 epidemiologic studies. Unfortunately, there is a large variability in the findings of these studies and, as discussed at length in Chapter VI, these studies have severe limitations. The discrepant results may be due to differing asbestos exposures (fiber type and morphology, concentration, duration), confounding factors (occupation, residence, personal habits), misclassification and others. Limitations are due to differing study designs and their underlying strengths, weaknesses and inherent biases, and inability to gather historical exposure information, among others. The ingestion animal study data base provides support for the qualitative position that asbestos, albeit perhaps certain types, sizes and under certain dose regimes, may pose a potential human risk. Three bioassays demonstrate that chrysotile and amosite produce benign and/or malignant tumors in rats, GI tract tumors being among the most prevelant seen. Taken as a whole, the animal data base covering different types and sizes of fibers (rats and hamsters primarily), with ~15 different researchers and many more specific individual bioassays do not present a consistant picture, however, of what the situation with animal tumorigenicity is. The animal evidence however, contributes to the qualitative concern for a potential human health hazard [one study NTP (1985) having characteristics suitable for dose-response analysis and subsequent cancer risk analysis].

Given that asbestos is regarded as a U.S. EPA Group A compound regardless of exposure pathway (ingestion or inhalation) the question of dose-response analysis, in order to estimate carcinogenic potency, is a separate and distinct consideration. For ingestion exposure, which is the focus of this document, the qualitative analysis to estimate possible human cancer risks is clearly less certain that the situation with risk assessment for inhalation exposure.

Quantification of Carcinogenic Effects

For the proper quantification of carcinogenic effects from drinking water exposure, there should be available adequate studies, either animal or human, characterizing the dose-response level of asbestos ingestion. In epidemiological studies of the effects of asbestos in drinking water, a possible excess incidence of GI cancers were evaluated as were morbidity or mortality rates for some other cancers. The duration of exposure ranged from <20 years (in Duluth) to >50 years (in Quebec); asbestos concentrations ranged from less than detectable limits to $1300 \text{x} 10^6$ fibers/ℓ. The studies did not indicate consistent excesses of cancer. In Duluth, no consistent type of excess cancer among residents was reported (Levy et al., 1976; Mason et al., 1974; Sigurdson et al., 1981). In Quebec, cancer mortality was evaluated in relation to asbestos in municipal water supplies. Some excess cancers observed in males were attributed to probable occupational exposure (Wigle, 1977; Toft et al., 1981). In Connecticut, tumor registry data indicated that there was no association between asbestos risk scores and GI tumor incidence (Harrington et al., 1978; Meigs et al., 1980). In San Francisco, there were inconsistent excesses of some cancers (Conforti et al., 1981; Kanarek et al., 1980; Tarter, 1981). In Puget Sound, a proportional incidence analysis, which compared length of residence, suggested an excess for some GI cancers (Polissar et al., 1982).

All of the above epidemiological studies had weaknesses. The most serious weakness evolved from the substantial problems in classifying exposure because population data rather than individual data were used. Errors in classification will tend to weaken any true association that may exist between asbestos in drinking water and health. Considering the problems in determining individual exposure, these studies cannot be used to evaluate dose-response.

However, occupational (inhalation) epidemiological studies have shown that occupational exposure to asbestos causes a marked increase in the incidence rates of lung cancer, pleural and peritoneal mesothelioma. The incidence rate of GI tract cancers in exposed workers is increased in ~20 studies. The consistency of an increased cancer risk at extrathoracic sites and its magnitude, either in absolute (observed-expected deaths) or relative (observed/ expected deaths) terms, was less for cancer at other sites than for lung cancer. As discussed earlier, 10/23 studies demonstrated the risk at a $p<0.05$ level of significance. A consistent relationship was observed between a greater GI cancer risk and an increased lung cancer risk in those studies where the overall lung cancer was elevated at the $p<0.05$ level of significance. For dose-response purposes, however, the uncertainty about dose to the GI tract, for instance, lends considerable uncertainty to the derivation of risk values.

The Subcommittee on Risk Assessment of the Working Group for the DHHS Committee to Coordinate Environmental and Related Programs reviewed the literature on cancer risks associated with the ingestion of asbestos and concluded that no direct, definitive risk assessment could be conducted at this time (Lemen, 1986).

Extrapolation from Human Inhalation to Human Ingestion. The U.S. EPA (1980) and the NAS (1983) have extrapolated the results of cohort studies of populations occupationally exposed by inhalation in order to estimate the risk associated with the ingestion of asbestos in drinking water. The Ambient Water Quality Criteria Document (U.S. EPA, 1980) and the Drinking Water and Health report (NAS, 1983) consider much the same data of occupationally exposed workers with GI tract cancers, but use a slightly different method of calculating the "additional lifetime cancer risk of 1 in 100,000." The estimated levels that would result in increased lifetime cancer risks of 10^{-5}, 10^{-6} and 10^{-7} calculated by the U.S. EPA (1980) are 300,000 fibers/ℓ, 30,000 fibers/ℓ and 3000 fibers/ℓ, respectively. Corresponding numbers for males calculated by the NAS are 110,000 fibers/ℓ, 11,000 fibers/ℓ and 1100 fibers/ℓ. The more restrictive NAS levels arise mainly from two different assumptions than those used by the U.S. EPA.

1. The NAS assumed that 30% of the inhaled fibers were subsequently swallowed, where the U.S. EPA assumed that 100% would be eventually cleared and ingested. (The assumption of 100% probably overestimates the percent ingested).

2. The NAS assumed a conversion factor of 50 for optical microscopy to transmission electron microscopy, where the U.S. EPA assumed a factor of 200.

The above extrapolation of the results of cohort studies of occupationally exposed populations to estimate the risk associated with the ingestion of asbestos are based on the following assumptions:

1. Inhaled fibers are swallowed and are responsible for the increased risk of GI cancer and peritoneal mesothelioma in persons occupationally exposed to asbestos.
2. The number of fibers 5 μm or longer detected by optical microscopy is ~1/200th (or ~1/50th) of the amount of fibers of all lengths that can be detected by electron microscopy.
3. The fiber size distribution is the same in occupational air and drinking water samples.
4. Exposure to waterborne asbestos is over a 70-year period.

Overall, the use of the GI tract cancer based risk estimates from the inhalation exposure pathway to predict a cancer risk for an ingestion exposure pathway (specifically drinking water) has considerable uncertainty as to its reasonableness. While the cancer incidence itself (response) is reliable in the relative sense, the ingested dose assumptions from the inhalation exposure can only be dealt with by assumption. There is a further uncertainty because it is not clear how the assumed dose regime would compare with that provided by a direct ingestion pathway, such as provided by drinking water. The risk estimates, thus, are viewed as of less uncertainty given the availability of an NTP animal study with more appropriate exposure, i.e. diet.

In the asbestos contaminated drinking water study in the San Francisco Bay area, lung cancer in males was found to be strongly associated with the asbestos in the water supply, even after adjustments for selection bias

(Kanarek et al., 1980). At this time, however, it is felt that such data do not support a quantitative estimate of risk from lung cancer due to ingested asbestos.

Extrapolation from Animal Ingestion to Human Ingestion. The animal studies data base seems to provide the best data for cancer risk estimation from ingestion exposure. The confidence in the dose response analysis is less than ideal, however, owing to lack of consistency in the responses seen across many studies. Still, the animal-based estimate is believed to be hypothetically more reasonable for drinking water purposes than any of the other approaches that have been used in the past (eg. EPA, 1980; EPA, 1986a; NAS 1983). As such, this section will present an estimate of upper-limit risk for asbestos by ingestion. The data base chosen to calculate the estimate is from a draft of the NTP (1985) ingestion study of chrysotile short-range (98% <10 μm in length) and intermediate range (65% >10 μm in length with 14% >100 μm) fibers (counts by TEM). The results of the NTP (1985) study showed no evidence of carcinogenicity for the short-range fibers in either male or female rats, and no evidence of carcinogenicity for the intermediate range fibers in the female rats. However, for the male rats ingesting the intermediate range fibers at 1% of the diet ad lib (or 10,000 mg/kg), benign epithelial neoplasms (adenomatous polyps) were observed in the large intestine at the incidence of 9/250 (3.6%).

> "Although not statistically significant (p=0.08) compared with concurrent controls (0/85), the incidence of these neoplasms was highly significant (p=0.003) when compared with the incidence of epithelial neoplasms (benign and malignant combined) of the large intestine in the pooled control groups (male) of all the NTP oral asbestos lifetime studies (3/524, 0.6%)" (NTP, 1985).

Based on these findings, the NTP claimed there was "some" evidence of carcinogenicity in male rats exposed to intermediate range chrysotile fibers.

In order to estimate a unit risk in drinking water for asbestos, an assumption must first be made that the asbestos in the dry diet would have the same effect as asbestos in water. In order to establish dose it is assumed that a rat consumes 5% of its body weight per day. The average body weight of this group of male rats at 52 weeks was 0.38 kg; this will be taken as the weight of the average rat. Thus, the daily dose is

$$(0.38 \text{ kg} \times 0.05)\ (10{,}000 \text{ mg/kg of diet}) = 190 \text{ mg (or } 500 \text{ mg/kg)}.$$

Based on measurements by TEM performed at the Illinois Institute of Technology Research Institute, the fiber counts/g were 0.1291×10^{12} (NTP, 1985) (or $\sim 0.129 \times 10^{9}$ f/mg) with a median fiber aspect ratio (length divided by diameter) of 8.435. Changing the daily dose to the number of fibers yields

$$500 \text{ mg/kg} \times 0.129 \times 10^{9} \text{ f/mg} = 6.45 \times 10^{10} \text{ f/kg}.$$

In order to determine human equivalent dose, the U.S. EPA procedure has been to assume dosage equivalency on a dose/surface area basis. This is roughly equal to equivalency on a dose/(body weight)$^{2/3}$. Thus, equivalent human dosage for a 70 kg human is

$$(6.45 \times 10^{10} \text{ f/kg})/(70/0.380)^{1/3} = 1.13 \times 10^{10} \text{ f/kg bw}.$$

Since a 70 kg human drinks ~2 ℓ of water/day this dose, in terms of drinking water, becomes

$$1.13 \times 10^{10} \text{ f/kg} \times 70 \text{ kg}/2 \ \ell = 4.0 \times 10^{11} \text{ f}/\ell.$$

Since there is only a control and one dose level, the usual linearized multistage model is reduced to a single dose or one-hit model. The maximum likelihood estimate (mle) of potency* is

$$q_1 = -\ln \frac{(1-P_t)}{(1-P_c)} \ /d = -\ln [(1 - 0.036)/(1 - 0.006)]/4.0 \times 10^{11} \text{ f}/\ell$$

$$= 7.7 \times 10^{-14} \ (\text{f}/\ell)^{-1}$$

with a 95% upper-limit potency

$$q_1{}^* = 1.4 \times 10^{-13} \ (\text{f}/\ell)^{-1}.$$

For a lifetime individual risk of 10^{-6}, the maximum likelihood estimate of concentration is 1.3×10^{7} f/ℓ with a 95% lower limit of 7.1×10^{6} f/ℓ. For individual lifetime risk of 10^{-5} to 10^{-7} the corresponding estimates are given below.

Lifetime Individual Risk	Maximum Likelihood Estimate of Fiber Concentration (f/ℓ)	95% Upper Limit of Fiber Concentration (f/ℓ)
10^{-5}	1.3×10^{8}	7.1×10^{7}
10^{-6}	1.3×10^{7}	7.1×10^{6}
10^{-7}	1.3×10^{6}	7.1×10^{5}

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*The potency and concentration estimates given in this section (mle and 95% confidence limits) are statistical estimates only under the assumption that the one-hit model is correct.

The above levels are calculated from the IR chrysotile fiber study. As such, the levels are much more restrictive than they would have been had they been calculated from the SR chrysotile fiber study. The SR study showed no effects with 50 times the number of fibers as the IR study. If the data from the SR study had been included with the data from the IR study using only the number of fibers, the resulting levels would have been at least 10 times higher (i.e., less restrictive) than the levels given above.

The IR study itself contained shorter fibers (although still within the defined IR), which in the SR study were shown to be noncarcinogenic. If these shorter fiber counts had been eliminated from the positive IR fiber study, the resulting levels would have been lower than those listed above by a factor of ~2.5.

Existing Guidelines and Standards

The current Occupational Safety and Health Administration (OSHA) standard for an 8-hour TWA occupational exposure to asbestos is 0.2 fibers/cc of air. This is for fibers >5 μm with an aspect ratio ≥3:1 as determined by the membrane filter method at 400-450X magnification phase contrast illumination (ACGIH, 1986). This standard has been in effect since July 21, 1986, when it replaced an earlier one of 2 f/cc (TWA). In Great Britain, a value of 1 f/mℓ is now the accepted level for chrysotile. This standard resulted from recommendations made by the Advisory Committee on Asbestos (1979), which also recommended a TWA of 0.5 f/mℓ for amosite and 0.1 f/mℓ for crocidolite (U.S. EPA, 1984). The previous standard, in effect from 1969 to 1983, was 2 f/mℓ (TWA) (BOHS, 1968). This earlier British standard, in fact, served as a guide for the OSHA standard (NIOSH, 1972). The British standard was developed specifically to prevent asbestosis among working populations; data were felt to be lacking that would allow for determination of a standard for cancer (BOHS, 1968). Unfortunately, among occupational groups, cancer is the primary cause of excess death for workers with three-fourths or more of asbestos-related deaths caused from malignancy. This fact led OSHA to propose a lower TWA standard to take into account carcinogenic effects. (Federal Register, 1986). With regard to health effects, the standard states "OSHA is aware of no instance in which exposure to a toxic substance has more clearly demonstrated detrimental health effects on humans than has asbestos exposure".

The existing federal standard for asbestos emissions into the environment prohibits either no visible emissions or employment of specified control techniques (U.S. EPA, 1975). No numerical value was specified because of difficulty in monitoring ambient air asbestos concentrations in the ambient air or in stack emissions. Some local government agencies, however, may have numerical standards (e.g., New York, 27 ng/m^3).

No standards for asbestos in foods or beverages exist even though the use of filtration of such products through asbestos filters has been a common practice in past years. Asbestos filtration, however, is now prohibited or limited for human drugs (U.S. FDA, 1976).

The recommended water quality criterion for asbestos calculated to keep the individual lifetime cancer risk below 10^{-5}, is 300,000 fibers of all sizes/ℓ. The corresponding mass concentration for chrysotile asbestos is ~0.05 μg/ℓ (U.S. EPA, 1980). The National Academy of Sciences (NAS, 1983) has also calculated the risk associated with the ingestion of 110,000 fibers/ℓ of asbestos fibers from drinking water based on risk from inhalation exposure data. This criterion is derived from the data that exists for the increased incidence of peritoneal mesothelioma and GI tract cancer in humans exposed occupationally to asbestos. This derivation assumes that much or all of this increased disease incidence is caused by fibers ingested following clearance from the respiratory tract. Several studies suggest the association of proximate airborne fiber concentrations to which individuals were exposed with observed excess peritoneal and GI cancer. All of the inhaled asbestos is assumed to be eventually cleared from the respiratory tract and ingested.

Special Groups at Risk

The effects of ingested asbestos on human populations have been examined based on the response of large exposed groups. To date, there have been no studies that have attempted to isolate or quantify the effects of asbestos ingestion on any specific subgroup within an exposed subpopulation to demonstrate increased susceptibility to adverse effects.

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APPENDIX

Assessment of Asbestos Studies with Respect to Fiber Type and Size

Introduction

It is well known that asbestos is not one but a family of fibrous minerals, each of which has distinctive physical and chemical characteristics. Minerals from various parts of the world and geologic formations often have dissimilar physical properties, even though they are classified under a specific mineralogic type. These differences are relevant to the understanding of the effects of asbestos on health, since the characteristics of the fibers have been fully defined in only a few experimental studies. The problem of evaluating the effects of different types of asbestos on health is compounded by the common practice of custom blending various minerals for a specific industrial application, and different analytical techniques for measurements of asbestos (mass vs. fibers).

The major pathologic effects of asbestos result from the inhalation of fibers suspended in the air. The occurrence of disease is influenced by the type of mineral and the dimensions of the fibers that constitute it, as well as by the concentration of fibers and the duration of exposure.

When nonfibrous compact dust particles are inhaled, the ones greater than ~5 μm in diameter are generally trapped in the nasal passage before reaching the respiratory system (Walton, 1982). However, the inhaled fibers align themselves parallel to the airways and act as spheres of approximately "equivalent" diameter (Gross, 1981; Timbrell et al., 1970). The equivalent or aerodynamic diameter of a particle is defined as the diameter of a sphere with a density of 1 g/cm^3 that has the same falling speed as the particle. There is no sharp cutoff of particle sizes determining their deposition site (Brain and Valberg, 1979).

Inhalation of Asbestos by Fiber Type

In occupational circumstance, the current method of quantitating asbestos air concentrations allows only for the enumeration of all fibers >5 μm collected on a specified area of filter, utilizing phase-contrast light microscopy (NIOSH, 1972). Also, a fiber of 0.19 μm diameter cannot be viewed, regardless of length since 0.2 μm is the lower limit of resolution (0.4 μm is more typical) for the most highly skilled microscopist. Such instrumentation does not allow for the identification of the fibers according to mineral type or size.

It is a well established fact that inhalation exposure of asbestos is associated with increased risks of lung tumors (bronchogenic carcinoma and peripheral adenocarcinoma), pleural and peritoneal mesothelioma, interstitial pulmonary fibrosis (asbestosis), pleural thickening and possible other tumors, including those of the GI tract and kidney. Investigators have induced lung tumors, mesotheliomas and fibrosis after administration of asbestos of animals. In some of these experimental studies in animals, the investigators have provided a description of the size and types of fibers used. For example, Lee et al. (1981) have shown that the inhalation of amosite (AM), fiber glass (FG) and potassium octantinate (Fybex) in rats and hamsters caused adenoma, carcinoma and mesothelioma over the 3 months of exposure. The reported length of Fybex fiber was >5 μm (Table A-1).

TABLE A-1

Respiratory Tract Tumors in Rodents After Inhalation of Asbestos and Other Asbestiform Fibers*

Fiber Type	(No. of Tumors/ No. of Animals	Animal	Tumor Types	Reference
AM, FG (fine), Fybex (>5 μm length), PKT	Experiment 1: AM (3/16), FG (2/19), Fybex (1/21) in rats, Fybex (1/12 in hamsters	Rat guinea pig, hamster	adenoma, carcinoma, mesothelioma	Lee et al., 1981
	Experiment 2: Fybex (3/25), Fybex (1/19), in rats, Fybex (2/16) in hamsters			
Alumina (medium length, 35-62 μm; diameter 1-5 μm) vs. CH (UICC)	Alumina = 0/60 CH = 5/38	rat	adenoma, squamous cell, adenocarcinoma	Piggott et al., 1981

*Source: Adapted from NAS, 1984

AM = Amosite; FG = fiberglass; Fybex = potassium octantinate, PKT = pigmentary potassium titanate, CH (UICC) = chrysotile (International Institute Against Cancer)

Table A-2 shows the occurrence of mesotheliomas appearing in rodents after injection of asbestiform fibers. This injection technique has been used most frequently in reported studies because of its reproducibility (NAS, 1984). Stanton et al. (1977, 1981) reported that tumor incidence was greatest for fibrous glass >8 μm in length. Wagner et al. (1973) observed in their experiments that fibers >10 μm in length were more tumorgenic than nonfibrous materials. From the data presented in Table A-2, it may be stated that exposure to long (>8 μm) fibers results in the appearance of mesotheliomas. Nonfibrous particles, including cleavage fragments, do not generally cause tumors.

Fibrosis, associated with asbestos and asbestiform fibers, has been experimentally produced in various animal studies. Table A-3 shows those studies for which fiber types have been reported by the investigators. The important features of these experiments can be summarized by stating that inhalation and pleural injection studies implicate the increased fibrogenic potential of longer (>10 μm) fibers of both asbestos and fibrous glass.

Fredricks (1979) also provides some interesting data concerning morphological aspects, namely the size and shape of fiber content in human lung dusts. The author observed that most of the fibers in the lung of the one asbestos worker were shorter than 20 μm in length and thinner than 1 μm. However, the majority of fibers in the samples of the analyzed groups (normal, mesothelioma cases and asbestosis plus mesothelioma) were shorter than 30 μm and thinner than 2 μm; the longest fibers were found to be 180 μm.

TABLE A-2

Mesotheliomas in Rodents Appearing after Injection of Asbestiform Fibers*

Mode of Administration	Dose (mg)	(No. of Tumors/No of Animals) or Percent Tumors by Fiber Exposure	Animal	Reference
Intrapleural or intrathoracic	one time CR = 1, 10, 40 mg on glass pledget	CH (15/30), AM (15/30), CR (14/30), milled CR (8/30), FG (1-25 µm diameter, 1/30), FG (0.06-3 µm diameter, 4/60), CR (at 1 mg, 2/40; at 10 mg, 11/40), pledget alone (0/40)	rat	Stanton and Wrench, 1972
	40 on glass pledget	17 samples of FG tested; greatest tumor incidence observed for FG >8 µm length, <1.5 µm diameter	rat	Stanton et al., 1977
	40, one time	CR, CH, FG, allminum oxide all <5 µm diameter, >50% tumors	rat	Stanton and Layard, 1978
	40, one time	Most fibers $\leq$0.25 µm diameter, >8 µm length were tumorigenic, but induction also observed for fibers <1.5 µm diameter, >4 µm length; 72 experiments	rat	Stanton et al., 1981
	0.5, 1, 2, 4, 8 (SFCH, CR); rest, 20, one time	Dose response: Tumors observed with SFCH, CH, milled CH, AM, AN, CR, brucite ceramic fiber, barium sulfate, FG, glass powder, aluminum oxide. Tumors were induced with nonfibrous materials, but more were seen with fibers >10 µm length, <5 µm diameter	rat	Wagner et al., 1973
	20, one time	CH (45%); leached (0-3%); CR (54%); leached fibers were shorter, thicker and there were fewer per unit weight	rat	Monchaux et al., 1981

TABLE A-2 (cont.)

Mode of Administration	Dose (mg)	(No. of Tumors/No of Animals) or Percent Tumors by Fiber Exposure	Animal	Reference
	1, 10, 25	CR: at 1 mg (2/50), at 10 mg (10/50); AM: at 10 mg (3/50); CH: at 1 mg (0/50), at 10 mg (4/50), at 25 mg (9/50); AM: at 1 mg (0/50), at 10 mg (4/50); talc at 25 mg (0/50), control 0/100); milled CH at 25 mg (<0.37 µm length, 0.07 µm diameter (0/150); fibrous nemalite at 25 mg (0/50); silicon dioxide at 10 mg (4/40), FG 50 µm diameter (0/50)	hamster	Smith and Hubert, 1974
	25, one time	Group 1: FG 0.1 µm diameter, 82% >20 µm length (5/60); Group 2: FG 0.3 µm diameter, 46% >20 µm length (2/60); Group 3: FG 1.23 µm diameter, 34% >20 µm (2/60); none in three groups of FG where 2% >10 µm length	hamster	Smith et al., 1980
Intraperitoneal	0.5, 2, 5, 10	Diversity of mineral fibers ≤20 µm diameter, <0.25 µm length; GF induction of tumors reduced with hydrogen chloride and NaOH treatment	rat	Pott et al., 1982

*Source: Adapted from NAS, 1984

CH = Chrysotile; CR = crocidolite; AM = amosite; FG = fibrous glass; GF = glass fiber; SFCH = superfine chrysotile

TABLE A-3

Development of Fibrosis in Animals after Inhalation or Intratracheal Instillation of Asbestos and Other Asbestiform Fibers[a]

Mode of Administration	Fiber Type	Concentration (mg/m³)[b] and Duration	Animal	Latency (months)[c]	Observations	Reference
Inhalation, instillation	GW 20-50 μm length and short fibers	NR	guinea pig	ND	No fibrosis	Schepers and Delahant, 1955
	CH, CR, AN, AM, TR, brucite, all long (20-50 μm) vs. short (<5 μm)	NR ≤ 3 years	rat, guinea pig, mouse, cat, dog	16 (guinea pig) 14 cat	Fibrous reaction: Guinea pig > rabbit = cat = rat > mouse and dog. Long CR fibers: fibrosis; long AM, CR, brucite → peribronchiolitis; long TR → bronchiolar fibrosis; AN → no fibrosis; no fibrosis with short fibers.	Vorwald et al., 1951
Combined inhalation and instillation	FG (0.5 μm diameter, 5-20 μm length)	100 24 months	rat, hamster	NA	Mild macrophage infiltration without fibrosis.	Gross et al., 1970, 1974
Instillation	Sized CR, CH, FG, synthetic fluoroamphibole	3-25 2-6 times	guinea pig	24	Minimal peribronchiolar fibrosis only with fibers >10 μm length.	Kuschner and Wright, 1976

[a] Source: Adapted from NAS, 1984

[b] Applied to inhalation exposures. Dose expressed differently for other types of exposure.

[c] From beginning of exposure

CH = Chrysotile; CR = crocidolite; AN = anthophyllite; AM = amosite; FG = fibrous glass; TR = tremolite; GW = glass wool

NA = Not applicable; NR = not reported

In summary, even though the interpretation of the experimental results of many asbestos and asbestiform studies regarding pathogenicity of various fiber types is complicated (because only the mass of asbestos administered was mentioned), the data presented in the preceding section suggest the following:

1. Respiratory tract tumors are observed in rats and hamsters following inhalation exposure to Fybex (potassium octantinate) >5 μm length (Table A-1) (Lee et al., 1981).
2. Inhalation exposure to long (>10 μm) fibers results in the appearance of mesotheliomas, (rats). Nonfibrous particles, including cleavage fragments, do not generally cause tumors.
3. Inhalation and pleural injection studies implicate the increased fibrogenic potential of longer (>10 μm) fibers of both asbestos and fibrous glass, (rats).

Ingestion of Asbestos by Fiber Type

There are few ingestion studies in which mineral and fiber characterization of asbestos fibers are reported (Table A-4). The results of bioassays of amosite (median length 4.37 μm, range 0.85-995 μm), and chrysotile short-range (SR, median length 0.66 μm, range 0.088-51.1) or intermediate-range (IR, median length 0.82 μm, range 0.104-783) did not demonstrate any carcinogenicity in hamsters when ingested over the lifetime period (McConnell et al., 1983b). In another ingestion study in animals, McConnell et al. (1983a) demonstrated that amosite asbestos with a median length of 4.37 μm (range 0.85-995) was not carcinogenic when ingested at a level of 1% in the diet by male and female rats.

The NTP (1985) has reported the results of a study on the carcinogenic potential of the ingestion of chrysolite short-range (98% <10 μm) and intermediate-range (65% >10 μm with 14% >100 μm) fibers. The results of the study showed no evidence of carcinogenicity for the SR fibers in either

TABLE A-4

Digestive Tract Tumors in Rodents after Administration of 1% in Diet of Abestos

Fiber Type	Dose in Diet Lifetime (%)	Fiber Size Length/Diameter		Digestive Tract Tumor		Animal	Reference
		Short-Range (μm)	Intermediate-Range (μm)	Short-Range (μm)	Intermediate-Range (μm)		
Chrysotile	1	0.088-51.1/ 0.019-1.57	0.104-783/ 0.019-11.5	ND	ND	hamster	McConnell et al., 1983[b]
Amosite	1	-	0.85-995/ 0.064-12.4	-	ND	hamster	McConnell et al., 1983[b]
Amosite	1	-	0.85-995/ 0.064-12.4	-	ND	rat	McConnell et al., 1983[b]
Chrysotile	1	0.088-51.1/ 0.019-1.67	0.104-783.4/ 0.019-11.5	ND	Not detected in females. Benign epithelial nodules in 9/250 males	rat	NTP (1985)

ND = Not detected

male or female rats, and no evidence of carcinogenicity for the IR fibers in the female rats. However, for the male rats ingesting the intermediate-range fibers at 1% of the diet, benign epithelial neoplasms (adenomatous polyps) were observed in the large intestine at the incidence of 9/250. Based on these findings, the NTP concluded that there was some evidence of carcinogenicity in male rats exposed to IR chrysotile fibers.

In summary, the results of bioassays of amosite asbestos (median length of 4.37 μm) and chrysotile asbestos (<10 μm in length) do not show carcinogenic potential in hamsters and rats when fed at 1% in the diet over the lifetime period. However, there is some evidence of carcinogenic potential associated with chrysotile asbestos fibers (65% >10 μm in length), in male rats over the lifetime exposure.

Epidemiologic Asbestos Ingestion Studies by Fiber Type

Marsh (1983) reviewed and evaluated epidemiological studies of ingested asbestos conducted in five areas of the United States and Canada for the definitiveness and applicability regarding the development of ambient water quality standards. Several methodologic weaknesses and limitations were found in each study, leading to the determination that no individual study or aggregation of studies exist that would establish risk levels from ingested asbestos. The author considered that one of the factors that may have attributed to considerable discrepancies might have been the characteristic of asbestos exposures in drinking water in various study populations. The type of asbestos and other pertinent information are provided in Table A-5. It is seen from the table that the chrysotile asbestos was present in water supplies of 4 of the 5 study populations.

TABLE A-5

Characterisitics of Asbestos Exposures in Drinking Water in Various Study Populations*

Characteristic	Duluth, MN	Connecticut	Quebec	Bay Area, CA	Utah	Puget Sound, WA
Type of asbestos	amphibole	chrysotile	chrysotile	chrysotile	chrysotile	chrysotile
Number of fibers/ℓ	$1.0\text{-}30.0\times10^{6}$	BDL-0.7×10^{6}	$1.1\text{-}1300\times10^{6}$	$0.025\text{-}35\times10^{6}$	NA	$7.3\text{-}206.5\times10^{6}$
Population exposed	100,000	576,800	420,000	3,000,000	24,000	200,000
Maximum duration of exposure, year	15-20	23-44	>50	>40	20-30	>40

*Adapted from Marsh, 1983

BDL = Below detectable limit

NA = Not available

Millette et al. (1980) in a review of the results of >1500 asbestos analyses from water supplies suggest that the average length of chrysotile fibers found in an asbestos cement distribution system was 4 µm, while the average fiber length of chrysotile fibers contributed to a water supply by natural erosion was 1 µm. Some size characteristics of asbestos fibers found in various water supplies are given in Table A-6.

In summary, an attempt is made to assess the size characteristics of asbestos/asbestiform fibers and their pathologic effects of various exposures. This report has delineated the various pathologic effects of asbestos/asbestiform fibers associated with inhalation, ingestion exposure and pleural injection. It is recognized that these studies were not carried out under rigid experimental conditions, and yet, even with these guidelines, the results of the experiments conclude that an asbestos fiber >10 µm plays a significant role in producing various effects.

Discussion

Lee et al. (1981) have shown that the inhalation of amosite, fiberglass and potassium octantinate in rats and hamsters caused adenoma, carcinoma and mesothelioma. The reported length of potassium octantinate fiber was >5 µm.

In other studies, Stanton et al. (1977, 1981) reported that tumor incidence in animals was greatest for fibrous glass >8 µm in length. Similarly, Wagner et al. (1973) also observed in their experiments that fibers >10 µm in length were more tumorgenic than nonfibrous material in animals (rats).

TABLE 6

Some Size Characteristics of Asbestos Fibers Found in Various Water Supplies[a]

Source	Type of Fiber	Number of Fibers (μm)	Average Length (μm)	Average Width (μm)	Average Aspect Ratio[b]	Maximum Length Found (μm)
Reservoir with natural erosion (WA)	chrysotile	289	0.8	0.034	25:1	3
Reservoir with natural erosion (CA)	chrysotile	644	1.3	0.04	39:1	10
Cistern with asbestos tile roof (VI)	chrysotile	342	2.3	0.04	62:1	25
Distribution sites from five asbestos cement pipe system (SC, PA, FL)	chrysotile	1440	4.3	0.044	121:1	80
Lake Superior (MN)	amphibole	468	1.5	0.18	11:1	14

[a] Millette et al., 1980

[b] Length/width

Data concerning fiber size in human lung dust in asbestos exposed workers (Fredricks, 1979) showed that the majority of fibers in the samples of the analyzed groups were in the range of 10-30 μm in length.

Lifetime asbestos ingestion bioassays for carcinogenicity in animals by McConnell et al. (1983a,b) and NTP (1985) provide some interesting information on the asbestos fiber size and its carcinogenicity in animals. McConnell et al. (1983b) reported no evidence of carcinogenicity of the GI tract in hamsters following administration of diet containing 1% amosite (median length 4.37 μm) or chrysotile asbestos consisting of short-range (median length 0.66 μm) or intermediate-range (median length 0.82 μm) fibers. The investigators also reported that ingestion of amosite consisting of a median length of 4.37 μm resulted in no GI tract carcinogenicity in rats.

NTP (1985) showed that intermediate-range chrysotile asbestos consisting of median length fibers of 0.82 μm (65% >10 μm; 14% $\geq$100 μm) was associated with causing benign epithelial neoplasms (adenomatous polyps) in the large intestine of male rats when fed at 1% in the diet. The short-range chrysotile asbestos (median length 0.66 μm; 98% <10 μm in length) had no effect on male or female rats.

Implication of the assessment of asbestos fibers >10 μm in length being responsible for observed carcinogenicity in animals and humans leads to:

1. The explanation why there was no clear evidence of GI tract cancer observed in the populations drinking water containing asbestos in the epidemiological ingestion studies.

2. The determination of excess lifetime cancer risk, if any, from the ingestion of chrysotile fibers >10 μm in length from drinking water contaminated with asbestos.

The reasons for the lack of increase in the GI tract cancer in the populations drinking water containing asbestos (epidemiological studies) may be that the fibers present in these water supplies were <10 μm in length. In support of this argument, the Marsh (1983) review of 13 epidemiological studies provides the asbestos "type" present in these water supplies and Millette et al. (1980) provide the size of asbestos fiber present in some of those water supplies of epidemiological ingestion studies. Marsh (1983) has stated that the asbestos "type" present in the water supplies of 4 out of 5 areas was chrysotile asbestos. Millette et al. (1980) in their review of results of >1500 asbestos analyses of water supplies of various areas (e.g., California, Washington, etc.), demonstrate that the average length of chrysotile asbestos in the asbestos cement distribution system was 4 μm, while the average fiber length of chrysotile asbestos contributed to a water supply by natural erosion was 1 μm. Therefore, these arguments strongly suggest that the lack of increase in GI tract cancer in the populations drinking water containing asbestos might be due to the majority of chrysotile asbestos being well below 10 μm in length.

With regard to determining excess lifetime cancer risk from ingestion of chrysotile asbestos >10 μm in length, the evidence of asbestos carcinogenicity of the GI tract is limited. As such, the data base chosen to calculate the estimate of risk (GI tract cancer) by ingestion is from an NTP

(1985) ingestion study of intermediate-range chrysotile asbestos >10 μm in length. Using this study, the estimated levels that would result in increased lifetime cancer risk (fibers/ℓ) of 10^{-5}, 10^{-6} and 10^{-7} are: 7.1×10^7, 7.1×10^6 and 7.1×10^5 fibers/ℓ, respectively.

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